chapter 1

What Is Nuclear Medicine?

A. FUNDAMENTAL CONCEPTS

The science and clinical practice of nuclear medicine involve the administration of trace amounts of compounds labeled with radioactivity (radionuclides) that are used to provide diagnostic information in a wide range of disease states. Although radionuclides also have some therapeutic uses, with similar underlying physics principles, this book focuses on the diagnostic uses of radionuclides in modern medicine.

In its most basic form, a nuclear medicine study involves injecting a compound, which is labeled with a gamma-ray-emitting or positron-emitting radionuclide, into the body. The radiolabeled compound is called a *radiopharmaceutical*, or more commonly, a *tracer* or *radiotracer*. When the radionuclide decays, gamma rays or high-energy photons are emitted. The energy of these gamma rays or photons is such that a significant number can exit the body without being scattered or attenuated. An external, position-sensitive gamma-ray "camera" can detect the gamma rays or photons and form an image of the distribution of the radionuclide, and hence the compound (including radiolabeled products of reactions of that compound) to which it was attached.

There are two broad classes of nuclear medicine imaging: *single photon imaging* [which includes single photon emission computed tomography (SPECT)] and *positron imaging* [positron emission tomography (PET)]. Single photon imaging uses radionuclides that decay by gamma-ray emission. A *planar* image is obtained by taking a picture of the radionuclide distribution in the patient from one particular angle. This results in an image with little depth information, but which can still be diagnostically useful (e.g., in bone scans, where there is not much tracer uptake in the tissue lying above and below the bones). For the tomographic mode of single photon imaging (SPECT), data are collected from many angles around the patient. This allows cross-sectional images of the distribution of the radionuclide to be reconstructed, thus providing the depth information missing from planar imaging.

Positron imaging makes use of radionuclides that decay by positron emission. The emitted positron has a very short lifetime and, following annihilation with an electron, simultaneously produces two high-energy photons that subsequently are detected by an imaging camera. Once again, tomographic images are formed by collecting data from many angles around the patient, resulting in PET images.

B. THE POWER OF NUCLEAR MEDICINE

The power of nuclear medicine lies in its ability to provide exquisitely sensitive measures of a wide range of biologic processes in the body. Other medical imaging modalities such as magnetic resonance imaging (MRI), x-ray imaging, and x-ray computed tomography (CT) provide outstanding anatomic images but are limited in their ability to provide biologic information. For example, magnetic resonance methods generally have a lower limit of detection in the millimolar concentration range ($\approx 6 \times 10^{17}$ molecules per mL tissue), whereas nuclear medicine studies routinely detect radiolabeled substances in the nanomolar ($\approx 6 \times 10^{11}$ molecules per mL tissue) or picomolar ($\approx 6 \times 10^{8}$ molecules per mL tissue) range. This sensitivity advantage, together with the ever-growing selection

of radiolabeled compounds, allows nuclear medicine studies to be targeted to the very specific biologic processes underlying disease. Examples of the diverse biologic processes that can be measured by nuclear medicine techniques include tissue perfusion, glucose metabolism, the somatostatin receptor status of tumors, the density of dopamine receptors in the brain, and gene expression.

Because radiation detectors can easily detect very tiny amounts of radioactivity, and because radiochemists are able to label compounds with very high specific activity (a large fraction of the injected molecules are labeled with a radioactive atom), it is possible to form high-quality images even with nanomolar or picomolar concentrations of compounds. Thus trace amounts of a compound, typically many orders of magnitude below the millimolar to micromolar concentrations that generally are required for pharmacologic effects, can be injected and followed safely over time without perturbing the biologic system. Like CT, there is a small radiation dose associated with performing nuclear medicine studies, with specific doses to the different organs depending on the radionuclide, as well as the spatial and temporal distribution of the particular radiolabeled compound that is being studied. The safe dose for human studies is established through careful dosimetry for every new radiopharmaceutical that is approved for human use.

C. HISTORICAL OVERVIEW

As with the development of any field of science or medicine, the history of nuclear medicine is a complex topic, involving contributions from a large number of scientists, engineers, and physicians. A complete overview is well beyond the scope of this book; however, a few highlights serve to place the development of nuclear medicine in its appropriate historical context.

The origins of nuclear medicine[1] can be traced back to the last years of the 19th century and the discovery of radioactivity by Henri Becquerel (1896) and of radium by Marie Curie (1898). These developments came close on the heels of the discovery of x rays in 1895 by Wilhelm Roentgen. Both x rays and radium sources were quickly adopted for medical applications and were used to make shadow images in which the radiation was transmitted through the body and onto photographic plates. This allowed physicians to see "inside" the human body noninvasively for the first time and was particularly useful for the imaging of bone. X rays soon became the method of choice for producing "radiographs" because images could be obtained more quickly and with better contrast than those provided by radium or other naturally occurring radionuclides that were available at that time. Although the field of diagnostic x-ray imaging rapidly gained acceptance, nuclear medicine had to await further developments.

The biologic foundations for nuclear medicine were laid down between 1910 and 1945. In 1913, Georg de Hevesy developed the principles of the tracer approach[2] and was the first to apply them to a biologic system in 1923, studying the absorption and translocation of radioactive lead nitrate in plants.[3] The first human study employing radioactive tracers was probably that of Blumgart and Weiss (1927),[4] who injected an aqueous solution of radon intravenously and measured the transit time of the blood from one arm to the other using a cloud chamber as the radiation detector. In the 1930s, with the invention of the cyclotron by Lawrence (Fig. 1-1),[5] it became possible to artificially produce new radionuclides, thereby extending the range of biologic processes that could be studied. Once again, de Hevesy was at the forefront of using these new radionuclides to study biologic processes in plants and in red blood cells. Finally, at the end of the Second World War, the nuclear reactor facilities that were developed as part of the Manhattan Project started to be used for the production of radioactive isotopes in quantities sufficient for medical applications.

The 1950s saw the development of technology that allowed one to obtain images of the distribution of radionuclides in the human body rather than just counting at a few measurement points. Major milestones included the development of the rectilinear scanner in 1951 by Benedict Cassen[6] (Fig. 1-2) and the Anger camera, the forerunner of all modern nuclear medicine single-photon imaging systems, developed in 1958 by Hal Anger (Fig. 1-3).[7] In 1951, the use of positron emitters and the advantageous imaging properties of these radionuclides also were described by Wrenn and coworkers.[8]

Until the early 1960s, the fledgling field of nuclear medicine primarily used ^{131}I in the study and diagnosis of thyroid disorders and an assortment of other radionuclides that were individually suitable for only a few specific organs. The use of ^{99m}Tc for imaging in

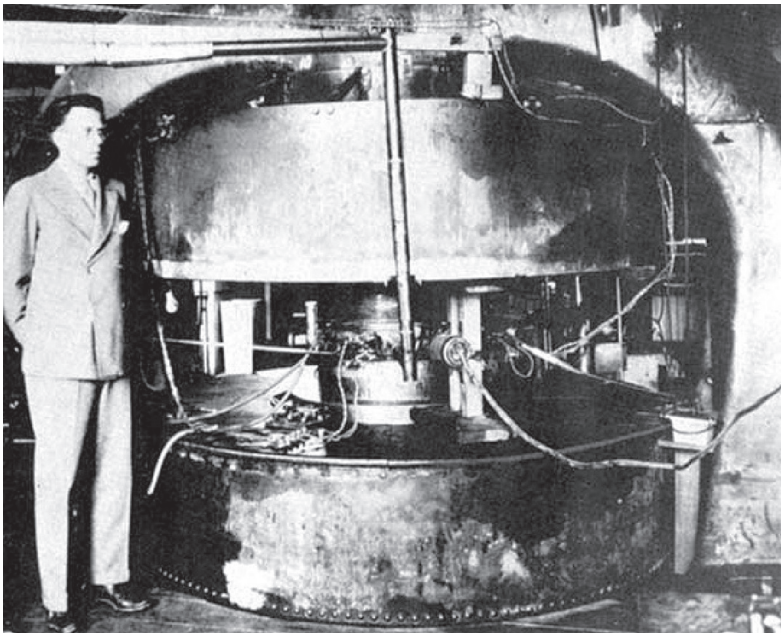

FIGURE 1-1 Ernest O. Lawrence standing next to the cyclotron he invented at Berkeley, California. (*From Myers WG, Wagner HN: Nuclear medicine: How it began.* Hosp Pract *9:103-113, 1974.*)

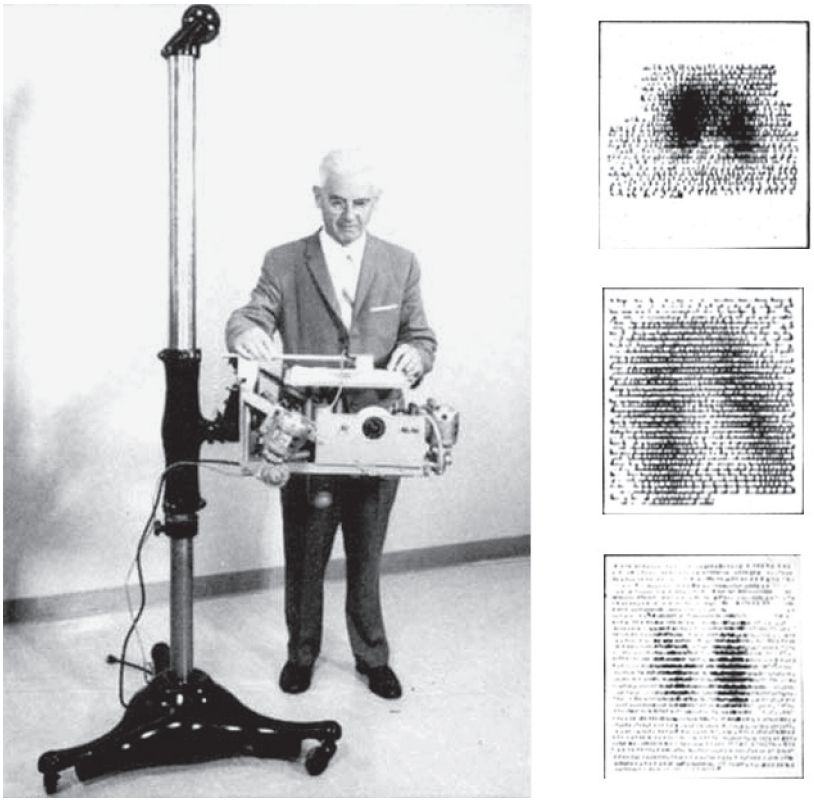

FIGURE 1-2 *Left*, Benedict Cassen with his rectilinear scanner (1951), a simple scintillation counter (see Chapter 7) that scans back and forth across the patient. *Right*, Thyroid scans from an early rectilinear scanner following administration of ^{131}I. The output of the scintillation counter controlled the movement of an ink pen to produce the first nuclear medicine images. (Left, *Courtesy William H. Blahd, MD; with permission of Radiology Centennial, Inc.* Right, *From Cassen B, Curtis L, Reed C, Libby R: Instrumentation for ^{131}I use in medical studies.* Nucleonics *9:46-50, 1951.*)

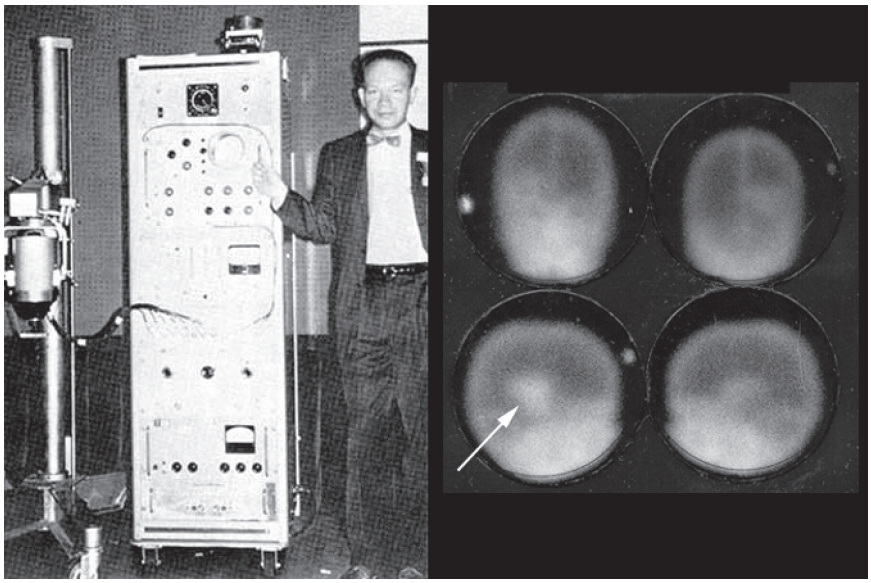

FIGURE 1-3 *Left*, Hal Anger with the first gamma camera in 1958. *Right*, ^{99m}Tc-pertechnetate brain scan of a patient with glioma at Vanderbilt University Hospital (1971). Each image represents a different view of the head. The glioma is indicated by an *arrow* in one of the views. In the 1960s, this was the only noninvasive test that could provide images showing pathologic conditions inside the human brain. These studies played a major role in establishing nuclear medicine as an integral part of the diagnostic services in hospitals. (Left*, From Myers WG: The Anger scintillation camera becomes of age.* J Nucl Med *20:565-567, 1979.* Right*, Courtesy Dennis D. Patton, MD, University of Arizona, Tucson, Arizona.*)

1964 by Paul Harper and colleagues[9] changed this and was a major turning point for the development of nuclear medicine. The gamma rays emitted by ^{99m}Tc had very good properties for imaging. It also proved to be very flexible for labeling a wide variety of compounds that could be used to study virtually every organ in the body. Equally important, it could be produced in a relatively long-lived generator form, allowing hospitals to have a readily available supply of the radionuclide. Today, ^{99m}Tc is the most widely used radionuclide in nuclear medicine.

The final important development was the mathematics to reconstruct tomographic images from a set of angular views around the patient. This revolutionized the whole field of medical imaging (leading to CT, PET, SPECT and MRI) because it replaced the two-dimensional representation of the three-dimensional radioactivity distribution, with a true three-dimensional representation. This allowed the development of PET by Phelps and colleagues[10] and SPECT by Kuhl and colleagues[11] during the 1970s and marked the start of the modern era of nuclear medicine.

D. CURRENT PRACTICE OF NUCLEAR MEDICINE

Nuclear medicine is used for a wide variety of diagnostic tests. There were roughly 100 different diagnostic imaging procedures available in 2006.* These procedures use many different radiolabeled compounds, cover all the major organ systems in the body, and provide many different measures of biologic function. Table 1-1 lists some of the more common clinical procedures.

As of 2008, more than 30 million nuclear medicine imaging procedures were performed on a global basis.† There are more than 20,000 nuclear medicine cameras capable of imaging gamma-ray-emitting radionuclides installed in hospitals across the world. Even many small hospitals have their own nuclear medicine clinic. There also were more than 3,000 PET scanners installed in the world performing on the order of 4 million procedures

*Data courtesy Society of Nuclear Medicine, Reston, Virginia.

†Data courtesy Siemens Molecular Imaging, Hoffman Estates, Illinois.

TABLE 1-1
SELECTED CLINICAL NUCLEAR MEDICINE PROCEDURES

Radiopharmaceutical	Imaging	Measurement	Examples of Clinical Use
^{99m}Tc-MDP	Planar	Bone metabolism	Metastatic spread of cancer, osteomyelitis vs. cellulitis
^{99m}Tc-sestamibi (Cardiolite) ^{99m}Tc-tetrofosmin (Myoview) ^{201}Tl-thallous chloride	SPECT or planar	Myocardial perfusion	Coronary artery disease
^{99m}Tc-MAG3 ^{99m}Tc-DTPA	Planar	Renal function	Kidney disease
^{99m}Tc-HMPAO (Ceretec)	SPECT	Cerebral blood flow	Neurologic disorders
^{99m}Tc-ECD	SPECT	Cerebral blood flow	Neurologic disorders
^{123}I-sodium iodide	Planar	Thyroid function	Thyroid disorders
^{131}I-sodium iodide			Thyroid cancer
^{67}Ga-gallium citrate	Planar	Sequestered in tumors	Tumor localization
^{99m}Tc-macroaggregated albumin and ^{133}Xe gas	Planar	Lung perfusion/ ventilation	Pulmonary embolism
^{111}In-labeled white blood cells	Planar	Sites of infection	Detection of inflammation
^{18}F-fluorodeoxyglucose	PET	Glucose metabolism	Cancer, neurological disorders, and myocardial diseases
^{82}Rb-rubidium chloride	PET	Myocardial perfusion	Coronary artery disease

MDP, methylene diphosphonate; MAG3, mercapto-acetyl-triglycine; DTPA, diethylenetriaminepenta-acetic acid; HMPAO, hexamethylpropyleneamine oxime; ECD, ethyl-cysteine-dimer; SPECT, single photon emission computed tomography; PET, positron emission tomography.

annually. The short half-lives of the most commonly used positron-emitting radionuclides require an onsite accelerator or delivery of PET radiopharmaceuticals from regional radiopharmacies. To meet this need, there is now a PET radiopharmacy within 100 miles of approximately 90% of the hospital beds in the United States. The growth of clinical PET has been driven by the utility of a metabolic tracer, ^{18}F-fluorodeoxyglucose, which has widespread applications in cancer, heart disease, and neurologic disorders.

One major paradigm shift that has occurred since the turn of the millennium has been toward multimodality instrumentation. Virtually all PET scanners, and a rapidly growing number of SPECT systems, are now integrated with a CT scanner in combined PET/CT and SPECT/CT configurations. These systems enable the facile correlation of structure (CT) and function (PET or SPECT), yielding better diagnostic insight in many clinical situations. The combination of nuclear medicine scanners with MRI systems also is under investigation, and as of 2011, first commercial PET/MRI systems were being delivered.

In addition to its clinical role, PET (and to a certain extent, SPECT) continues to play a major role in the biomedical research community. PET has become an established and powerful research tool for quantitatively and noninvasively measuring the rates of biologic processes, both in the healthy and diseased state. In this research environment, the radiolabeled compounds and clinical nuclear medicine assays of the future are being developed. In preclinical, translational and clinical research, nuclear medicine has been at the forefront in developing new diagnostic opportunities in the field of molecular medicine, created by the merger of biology and medicine. A rapid growth is now occurring in the number and diversity of PET and SPECT molecular imaging tracers targeted to specific proteins and molecular pathways implicated in disease. These nuclear medicine technologies also have been embraced by the pharmaceutical and biotechnology industries to aid in drug development and validation.

E. THE ROLE OF PHYSICS IN NUCLEAR MEDICINE

Although the physics underlying nuclear medicine is not changing, the technology for producing radioactive tracers and for obtaining images of those tracer distributions most certainly is. We can expect to continue seeing major improvements in nuclear medicine technology, which will come from combining advances in detector and accelerator physics, electronics, signal processing, and computer technology with the underlying physics of nuclear medicine. Methods for accurately quantifying the concentrations of radiolabeled tracers in structures of interest, measuring biologic processes, and then relaying this information to the physician in a clinically meaningful and biologically relevant format are also an important challenge for the future. Refinement in the models used in dosimetry will allow better characterization of radiation exposure and make nuclear medicine even safer than it already is. Physics therefore continues to play an important and continuing role in providing high-quality, cost-effective, quantitative, reliable, and safe biologic assays in living humans.

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