

Anniversary Paper: Nuclear medicine: Fifty years and still counting

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The history, present status, and possible future of nuclear medicine are presented. Beginning with development of the rectilinear scanner and gamma camera, evolution to the present forms of hybrid technology such as single photon emission computed tomography/computed tomography (CT) and positron emission tomography/CT is described. Both imaging and therapy are considered and the recent improvements in dose estimation using hybrid technologies are discussed. Future developments listed include novel radiopharmaceuticals created using short chains of nucleic acids and varieties of nanostructures. Patient-specific radiotherapy is an eventual outcome of this work. Possible application to proving the targeting of potential chemotherapeutics is also indicated. © 2008 American Association of Physicists in Medicine. [DOI: [10.1118/1.2936217](https://doi.org/10.1118/1.2936217)]

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I. ORIGINS AND ASSOCIATED CONSTRAINTS

I.A. Radionuclides

Nuclear medicine relies on the utilization of photons (both x ray and gamma) in the radiodecay scheme such that radioactive material can be detected from outside a patient or tissue sample. Applications of radioactive elements to physiology and medicine currently depend on man-made radionuclides. Originally, activity was provided by the decay products in the purified ores of radium and uranium. In his Nobel Prize work, Hevesy¹ did early plant circulation experiments in the 1920s involving radiolead. The story is told that he used this technology to prove that his landlady in Paris was recycling food to her boarding house guests. Sensitivity is exquisite. In principle, a single decay may be detected so that a single molecule or other labeled entity is recorded. Alpha and beta radiation are not amenable to external detection and are usually associated with radiotherapy. One exception is the use of positron (e^+) emitters to provide two 511 keV photons following annihilation in the sample.

With the development of atomic reactors and accelerators by physicists in the 1940s, many artificial radionuclides were produced to greatly expand the list of possible radiolabels. Most important among these were ^{99m}Tc and ^{131}I . While both are still heavily used in imaging, ^{131}I has been the prototype for tissue-specific (thyroid) radiotherapy. It was originally hoped that other tissue-specific therapies dependent upon use of single isotopes would develop out of this enhanced production, but that objective has largely been unfulfilled. In the 1970s, accelerator production of ^{18}F and other proton-excess radionuclides enabled the growth of positron-emission tomographic (PET) imaging

Two limitations in the choice of labels occur. First, the physicist must find an emitter that can be attached to or substituted into the agent of interest using one of the three methods outlined below. In addition, the physiological kinetics ($T_{1/2b}$)—particularly of the blood curve—had to be com-

parable to the physical half-life ($T_{1/2p}$) of the emitter chosen. Many positron emitters that appeal to our natural instincts such as ^{11}C , ^{15}O , and ^{13}N have half-lives that are on the order of 20 min or less so as to preclude their use in following relatively slow-moving tracers. Correspondingly, long-lived labels are not appropriate for rapidly moving agents due to radiation risks.

I.B. Types of labeling

There are three labeling methods available for radionuclide applications in living tissues. The investigator may use the radioelement directly as a substitute for the stable atomic element; e.g., ^{131}I for ^{127}I in following the body's use of iodine. Alternatively, the label may be inserted into the appropriate molecule in a direct isotopic switch as in the use of ^{11}C instead of ^{12}C in a protein of interest. A variant on this method is to use a radioelement from the same column of the Periodic Table. Today, in what has become the most common strategy, radiolabels are chemically attached to some man-made structure as exemplified by ^{111}In bound by a chelator that is, in turn, attached to an intact antibody.

Activity may become detached from the targeting agent. A liberated label may subsequently be free as an ion or even attached to another entity within the patient. Iodinated compounds particularly suffer from this possibility due to the presence of dehalogenation enzymes in normal and malignant mammalian tissues. These enzymes work to obtain iodine, of whatever atomic weight, for the thyroid. Their signature is appearance of the stomach and thyroid on subsequent nuclear images.

Breakdown of the chemical moiety may also occur during preparation or later inside a living system. In the former case, radiolysis is possible due to elevated concentration of activity (radiation dose) in a preparation step. Generally, this possibility can be tested for prior to injection. Metabolism is a definite concern *in vivo* whereby the injected radiopharmaceutical (RP) is changed into breakdown products that have

unintended cellular targets. Such changes may be much more difficult to detect. Metabolism is particularly important for agents that are based on short strands of RNA and DNA where nucleases exist in the blood to recycle these cell memory components. Generally, the sequence of bases in the agent is important so that any such changes would be detrimental to their intended molecular binding.

For physicists estimating absorbed dose, loss of label and/or metabolic alterations are generally not of concern since it is only the location of the radioactivity that is significant and not its presence in a given structure. For pharmacokinetic (PK) analyses, on the other hand, it is important to differentiate between activity on various molecules or other entities within the patient. Thus, the physicist's reported dose estimates may, in fact, refer not to the nominal agent injected but rather to its various (unknown?) metabolic products.

I.C. Target access

An additional constraint is placed on a putative nuclear agent. Arrival at the target tissue is usually accomplished via the bloodstream following IV injection. If the blood curve of the radiotracer decreases too rapidly, there may be little chance of targeting to sites of potential interest. It may be that the molecular form or structure destines the agent to be rapidly sequestered by the renal or hepatic systems. Additionally, the decay of the label may be so rapid that the tracer is lost to imaging as described above for common positron labels such as ^{11}C . Thus, one of the primary PK results of any novel radiopharmaceutical is its initial biological half time in the blood. In the case of tumors, there may be additional constraints due to peculiarities of blood supply or necrotic changes to the lesion's vasculature.

I.D. Target identification

Nuclear imaging has always had one basic problematic issue. While intense (hot) areas relative to a less-intense (cold) background can be detected, their actual organ source was often uncertain. This ambiguity has been a critical limitation of nuclear imaging and therapy for more than 50 years and led to the popular epithet "unclear medicine." As compared to planar x-ray or computed tomography (CT) results, the nuclear image is indeed more ambiguous due to increased image noise and poorer spatial resolution. As we will see below, the identification issue has logically led to the development of hybrid imagers that combine tomographic nuclear and anatomic results—usually based on CT imaging.

II. EVOLUTION OF NUCLEAR MEDICINE

II.A. Radiopharmaceutical development

Nuclear imaging and therapy depend directly on the existence of molecules and structures ("agents") that target particular tissues or tumor sites. Originally, such entities were discovered by accident or were relevant organic molecules. Today, reliance upon use of natural constructs is being lifted; e.g., by using recombinant DNA technology to allow novel

proteins to be produced. Whatever their origin, it is intended that these structures utilize readily available labels such as radioiodines and radiometals. As we will see below, use of simple gamma emitters as well as positron emitters are included in the designs. There is a strong intellectual parallel between chemical manipulation of materials in the contemporary nuclear pharmacy and production of artificial radioactivity in the era after World War II.

II.B. Instrumentation and imaging methods

While gas-based detectors dominated in early years and are still used in dose calibrators and protection instruments, scintillation counters were developed to permit higher efficiency photon detection. Both NaI(Tl) and CsI(Tl) crystals were generated by the late 1940s. Originally, a single such probe was set up beside the patient and counts of the whole body or organ site obtained using cylindrical collimation. Eventually, solid-state detectors such as Si(Li) and Ge(Li) were developed by physicists to allow smaller detectors with better counting statistics. Their use is limited by noise at room temperatures, which implies a need of detector cooling for these two materials.

Counting using the simple scintillator or solid-state detector relies on circuitry that allows the pulse to be recorded only if it lies between two predefined energy limits. For photoelectric detection, these are usually set symmetrically around the maximum photon energy; those events giving either too low or too high a value are not counted as they are assumed to be either above or below the energy of interest respectively. If the radiodecay is essentially a single photon event, this situation is not complicated unless multiple gammas hit the detector at essentially the same time. For multiple photon emitters such as ^{131}I , however, the use of a single energy window will necessarily include Compton scattering events of other photon energies. These may confound the counting (and thus the imaging) process.

In 1951, UCLA physicist Cassen² moved a NaI(Tl) probe and its focused collimator over the patient in raster fashion to obtain a single analog tomographic scan. This rectilinear scanner was the first imaging device developed in the field. Patient movement during scanning was a major issue and motivated invention of the gamma camera by physicist Anger³ at the Lawrence Radiation Laboratory in the 1950s and 1960s. Anger's localization technique depended upon an array of hexagonally close-packed photomultiplier tubes to locate each scintillation within a single large crystal of NaI(Tl). Because the patient is a volumetric source, it is necessary that Pb or W collimators be placed between the camera's single detector crystal and the patient to establish photon direction. The most common of these grids is the parallel-hole type that projects an unmagnified nontomographic image onto a relatively large crystal. Spatial coordinates of the photon's impact point (x , y) were originally determined using analog electronics measuring the set of signals from the array of photomultiplier tubes. Today, this triangulation process is done via computers within the camera head.

Because of its ability to do entire organ and dynamic imaging, gamma cameras replaced rectilinear scanners by the late 1960s. Clinically, there has been a tendency to increase the detector size of the camera to allow more of the patient to be viewed at one time. This has been achieved in two ways; employing larger single NaI(Tl) crystals and using more than one detector head simultaneously. Triple-head cameras have been produced. Today, the most common system is a dual-headed camera with each head being approximately 35×50 cm in size. Outside the clinic and in research contexts, small cameras continue to have some important applications. Some of these have been used as mobile units and very small heads are employed today in animal imaging.

Probably the most remarkable evolutionary feature of nuclear techniques has been continuing improvement in tomographic imaging starting from Cassen's pioneering efforts. Initial theoretical analyses were done by the mathematician Radon⁴ and physicist Cormack⁵ who independently realized that a three-dimensional (3D) object could be represented as a sum of its transmission line integrals. Initial research applications, in fact, were in nuclear imaging by radiologist Kuhl and co-workers⁶ at the University of Pennsylvania using a dedicated ring system of detectors. Commercial applications came via x ray when the prototype CT scanner was patented by Hounsfield⁷ of EMI in the early 1970s. The Nobel Prize in Medicine and Physiology in 1979 was awarded to physicists Cormack and Hounsfield for their work. Extension of the concept to planar gamma camera images occurred in the middle 1980s with the invention of single photon emission computed tomography⁸ (SPECT). Here emission data from a number of planar camera images taken around the patient were used to form sets of transaxial tomographic images.

Initial work on positron imaging was done by Brownell⁹ at Harvard using paired scintillators in the 1950s. By the 1970s, physicists Ter Pegossian, Phelps, and Hoffman¹⁰ at Washington University implemented positron emission tomography (PET) using a fixed set of ring detectors and the geometric constraint provided by e^+ emission. As computing power improved, PET images could be formed in either two-dimensional (2D) (with collimators) or in multiple section (3D) acquisitions. In the latter case the observer could dispense with collimation and simply use the simultaneous, back-to-back, 511 keV photons to define a geometric axis along which the positron decay had occurred. If the time resolution is sufficient, the location along that line is also evaluable. This technique was inherently tomographic with one to two orders of magnitude higher sensitivity compared to the collimated Anger camera.

For any nuclear imaging device to be practical there must be readily available radiolabels that do not require local nuclear physics equipment such as reactors or accelerators. In the case of gamma cameras, the ^{99}Mo – $^{99\text{m}}\text{Tc}$ generator, developed by Richards¹¹ at Brookhaven National Laboratory and popularized by Harper,¹² has been a vital part of the field's expansion since the 1960s. Using ^{99}Mo ($T_{1/2p} = 66$ h) from a fission reactor, chemists bind the starting ma-

terial to an alumina column inside the generator or "cow." Technetium is then eluted in the clinic by the radio pharmacist using a saline flush. The single 140 keV photon from $^{99\text{m}}\text{Tc}$ has also been appropriate for typical camera NaI(Tl) crystal thicknesses of 6–8 mm. The 6 h half-life, while short for some targeting agents, is usually adequate for one or more imaging sessions; e.g., in the bone scan. A comparable label for PET imaging has been ^{18}F , with a 110 m half-life. This value allows production at a relatively distant cyclotron and land transportation to the clinic for use—usually as ^{18}F -FDG, fluorodioxylucose. Taken together, these two radionuclides probably account for more than 90% of all clinical labeling.

Hybrid imaging devices have recently been developed which allow direct image fusion between tomographic nuclear and CT images. In such instruments, location of the radioactivity is more readily attributable to a specific anatomic site within the patient. Presently, both gamma camera (SPECT/CT) (Ref. 13) and positron emitter (PET/CT) (Ref. 14) technologies are commercially available to clinical imaging departments. Hybrids involving PET and magnetic resonance imaging (MRI) are also being tested.¹⁵ In the case where a hybrid is not yet installed or invented, the observer may attempt such fusions using software. The latter involves rotation/translation of the image pairs to achieve the most probable correct alignment.

II.C. Time analyses

II.C.1. General data acquisition

Unlike most x-ray results, nuclear imaging is intrinsically involved with the pharmacokinetics of its radioactive contrast agents. Although the nuclear radiologist might not have been able to uniquely identify any intense sources imaged, there were ample opportunities to follow such regions over time! Multiple serial images are then used as a basis for understanding the physiological function of the patient as the tracer moves through the blood and other tissues.

In the early days of computer applications in nuclear imaging, both list and frame mode acquisitions were possible. In the former case, a recorded event contained its x , y , and t (time) values. List mode data sets could then be constructed in any time frame that was equal to or greater than that of the clock cycle used in the acquisition. In the early 1970s, list mode would be used for first-pass recording of activity moving through the patient's heart. Memory requirements are considerable for list mode, so that this method is not typically available to present-day camera users. Frame mode, whereby only the x and y coordinates of photon impact are available from memory has become the standard acquisition technique for gamma cameras and most PET systems.

Time-activity curves resulting from the temporal analyses were modeled in one of two ways. An analyst could fit each curve with a multiexponential function; this is termed an open model and makes no assumptions *re* the interaction of tissues with each other. Such a computation is used, for example, in determining the residence time of the radioactivity for absorbed dose estimation as described below. Closed

models, on the other hand, are based on a set of differential equations that relate one organ's activity to another's with the blood generally given as the central compartment. Resultant rate constants can be used to describe how the agent moves from blood to tissue and back again.

II.C.2. Cyclical or gated acquisitions

A second and very important use of camera or probe counts, developed by physicists at NIH,¹⁶ was to electronically gate data synchronously with a physiological signal. The most common application uses the EKG cycle to obtain a set of a few (16–32) images of the left ventricle (LV) blood content. Referred to as multiple gated acquisitions (MUGA studies) the resultant curves were characteristic of hundreds of cardiac beats and could be analyzed using open modeling to define LV ejection fraction. Here, the observer generated a region of interest that encapsulated the LV following injection of a blood-pool agent such as the patient's ^{99m}Tc-labeled red cells. While generally done with planar imaging, SPECT-based MUGA studies are also possible.

II.C.3. Functional imaging

One of the most creative uses of nuclear kinetic information has been the invention of functional images. Here, in a geometric format, the analyst presents a set of numbers that denotes the quantitative behavior of a tissue of interest. For example, the uptake of blood-borne radioactivity by the brain may be analyzed using model-derived rate constants that are generated on a region-by-region basis. By showing these values in geometric registration with image data, the neurologist or vascular surgeon can determine which geometric volumes are relatively poorly perfused and may have been affected by stroke.¹⁷ In a sense, this result is a fused pair since the functional and direct images are automatically superimposed. It was through such imaging that the discovery was made concerning the variation of brain blood flow as a function of mental processing. Now this result has progressed to MRI applications whereby the patient performs various physical or mental tasks while having their brain imaged.

II.D. Absorbed dose estimation

Radiation dose estimation¹⁸ has been a legally required aspect of nuclear clinical protocols since the field's inception in the 1950s. In applying for regulatory approval of a clinical phase I study, the physicist must provide a set of organ-specific doses for any novel radiopharmaceutical. Usually these values are based on animal biodistribution data obtained with the same agent and label. Geometry of the human calculation is assumed to be that of a standard phantom of the appropriate sex. By the 1970s, the standard format of this total organ dose (D) computation was

$$D = S * \tilde{A}, \quad (1)$$

where the S matrix (cGy/MBq s) contained geometric, energy and emission properties while the \tilde{A} vector (MBq s) was

a set of integrals to infinity of time-activity curves for the several source organs

$$\tilde{A} = \int A(t)dt. \quad (2)$$

Various software systems, such as MIRDOSE (Ref. 19) and OLINDA,²⁰ have been developed by Stabin and his associates at ORNL and Vanderbilt University to expedite calculations with both equations. Computed values can then be readily checked by agencies such as the FDA. We will denote these phantom-based results as type I dose estimations.²¹ Note that the result is the average dose to the target and does not include voxel-based information.

A second, and equally important, estimate has been developed over the past 10 years—calculated internal emitter dose for a specific patient.²² In this type II calculation,²¹ particular geometric data on the size of the patient's major organ systems and even their separation are used to provide a set of dose values for that individual. Differences between the sizes of organs such as liver and spleen can be several fold as compared to phantom values.²³ If one deals with therapy protocols involving emissions that stop in the source organ, doses are inversely proportional to the tissue mass. Thus, the S matrix differences may be as large as factors of 2 or 3 when comparing the result of a type II computation to phantom-based results. These corrections are crucial in therapy trials where the radioactivity may cause collateral toxic effects in normal tissues such as red marrow, kidneys, and liver.

Beside the uncertainty in S , a second limitation on use of Eq. (2) is that no optimal method is available to determine activity (A) at depth in the patient. This is essentially the tomographic reconstruction issue with an attendant requirement that the result be quantitative in units of MBq. Because of this uncertainty, nuclear radiologists often read images with a qualitative set of values relative to a highly visible tissue such as the liver. Thus, activity as intense as the hepatic result may be quoted as a "1," somewhat higher is quoted as a "2" and so on up to a maximum of "4." No numerical results are given. Clearly, a significant amount of information has been lost or simply overlooked in such reports.

Early physics investigators of this issue such as Sorensen²⁴ and Thomas²⁵ in the 1970s advocated a geometric mean (GM) analysis to obtain absolute activity results for single sources at depth. Here counts were obtained from opposite (usually anterior and posterior) sides of the patient and the GM used to give a best estimate of the activity present. Besides possible misidentification (as noted above) of the tissue, other limitations included the problem of organ overlap; e.g., the juxtaposition of the right kidney and the liver. Moreover, even in simple single source testing using phantoms or animals of moderate size, uncertainties in the GM method have been shown to be approximately $\pm 30\%$ for ¹¹¹In, a common label for antibody studies.²⁶ While possibly adequate for imaging dose estimates, such uncertainties are generally not acceptable in radionuclide therapy.

II.E. Nuclear medicine therapy

Imaging has never been the sole function of nuclear medicine. Over the past half century, there has been continuing interest in agents that preferentially target to a malignant tissue. Thyroid treatment post-thyroidectomy is the classical protocol where sufficiently large activities of Na^{131}I are given by mouth to the patient.²⁷ To prove targeting and perhaps estimate radiation dose, a prior ingestion of Na^{123}I may be used along with probe uptake measurements and/or camera imaging. A similar application is the use of metaiodobenzylguanidine²⁸ (^{131}I -MIBG) to treat pheochromocytoma and other neuroendocrine tumors. These two standard techniques remain of interest in current practice.

A great effort has been expended over the past 25 years to develop very specific agents that target only to tumor-associated antigens (no tumor-specific antigen has yet been discovered). Originally, monoclonal antibodies (Mabs) were generated using hybridomas grown in mice. Today, these originally murine monoclonal antibodies have been partially, if not completely, transformed into human types. This development, based on DNA technology, was required as the purely murine forms eventually elicited immune responses in the patients due to their origins in an alien species. Both ^{131}I and ^{90}Y have been the radionuclides of choice to deliver the radiation dose to the malignant tissues. In the former case, imaging may be done with the therapy RP prior to treatment. If a ^{90}Y -Mab is of interest, the corresponding ^{111}In -Mab is generally employed as the imaging agent to prove targeting and attempt to estimate absorbed dose.

Beginning with colloids and liposomes, there has been recent, growing interest in the manufacturing of what may be termed nanoparticles. These are small—perhaps on the 50–100 nm scale—chemical moieties that can be directed to tissues of choice. One application, which is dependent upon construct size, is to pass through fenestrations in the walls of tumor vasculature. Stable liposomes of approximately that size have been applied to deliver radionuclides and chemotherapeutics into solid tumors.

III. CURRENT STATUS OF NUCLEAR MEDICINE

III.A. Nuclear counting and imaging

III.A.1. Probe (1D) counting

A classical use of the scintillation detector remains the counting of patient tissues *in vivo* and of samples *ex vivo*. Rudimentary cylindrical collimation is provided to give a limited field of view that may circumscribe a given organ or the entire patient for whole body evaluation. In the former case, thyroid assay remains a standard protocol following ingestion of a ^{123}I capsule. Relative uptake is evaluated over time and compared to euthyroid values to establish the organ's performance. A very important oncological application of single probes is in the location of major ("sentinel") lesion-draining lymph nodes during breast, melanoma, or other surgery.²⁹ Here miniaturization implies use of a room temperature, solid-state detector such as CdTe.²⁹ Such "hot nodes" are detected following the prior injection of

$^{99\text{m}}\text{Tc}$ -labeled sulfur colloid particles into the lymphatic bed by the surgeon. Upon removal, excised nodes are evaluated by the pathologist for signs of metastatic disease.

III.A.2. Planar (2D) imaging

Gamma camera applications are applicable in many disease evaluations. One of the most important is evaluation of the skeleton using a phosphate-based bone seeker such as $^{99\text{m}}\text{TcMDP}$. Here the camera-associated computer system generates a single image digitally stitched together from a number of contiguous rectangular images obtained while moving the two camera heads at a constant speed over (and under) the patient. Renograms, using ^{111}In held inside the chelator DTPA, are a second classical example of the method whereby comparisons are made between the patient's result and certain clearance standards. Likewise, serial studies may be made on the same individual following a therapeutic intervention.

A second very common application is determination of cardiac function using $^{99\text{m}}\text{Tc}$ -labeling of the patient's own red cells. Left ventricle ejection fraction (LVEF) is calculated using regions of interest on the ventricle and beside it. The exam is done as a MUGA using the patient's cardiac cycle to place images into a given set of cyclical time bins as described above.¹⁶ Resultant ejection fractions are then compared with tabular values for normal patients and disease states. This test is of vital importance if the individual is undergoing chemotherapy that causes cardiac muscle destruction.

III.A.3. Tomographic (3D) imaging

By rotating the gamma camera heads around the patient, one may obtain sufficient 2D projections (e.g., 60) to generate a set of tomographic sections through the volume of patient being circumscribed by the detectors. A very common application is myocardial evaluation using ^{201}Tl or MIBI labeled with $^{99\text{m}}\text{Tc}$. Cold areas in the resultant tomographic images may be interpreted as regions of reduced cardiac blood flow. Results are generally obtained at rest and with exercise to see if perfusion is a function of the physiological situation.

If a suitable radiopharmaceutical is at hand, positron emission tomography may be employed on a regional or whole-body basis. Multiple coaxial rings of BGO or LSO detectors are used to surround the patient and produce a number of tomographic sections simultaneously. Two detection modes are applied; 2D and 3D. In the former, Pb septae are used to separate the rings and each transaxial section is determined in isolation from the others. With 3D imaging, all of the rings may have coincidences with the others to generate more projection data in a given time. Since the sensitive volume of the PET camera is usually on the order of 20 cm, multiple stepwise imaging segments are needed to obtain large organ or whole-body images.

The most common PET scan is the ^{18}F -FDG application in patients with suspected malignant disease.³⁰ Metabolism by the tumor is assumed to utilize such sugar-like molecules.

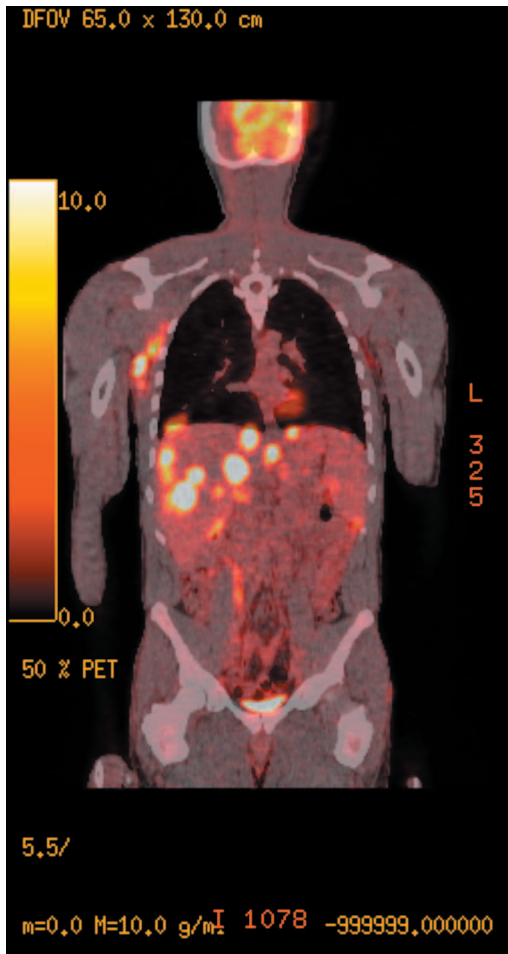


FIG. 1. A non-Hodgkin's lymphoma patient is shown. The anterior coronal PET/CT section shows intense FDG uptake in multiple sites in the liver and along the right side of the chest wall and axilla. Anatomic localization of activity is made clearer by reference to the background CT information included in this hybrid image.

Usually chest, abdomen, and pelvis are imaged to look for possible sites. This imaging protocol is becoming common during the following of a cancer patient during chemical or external beam radiation therapy to check disease status. Sites of infections and normal uptake by the brain are confounding issues.

III.A.4. Hybrid imaging methods

In the case of SPECT/CT, a CT scanner is mounted coaxially with an opposed pair of gamma cameras.¹³ Monitor images often use gray scales to represent CT and color to represent nuclear data sets, respectively, on the combined (fused) images. It is important to emphasize the future application of this technology by physicists in the estimation of organ radiation dose. Because the photon attenuation may be corrected for directly by use of Hounsfield numbers, uptake measurement in percent-injected dose per gram of tissue (%ID/gm) may be made with greater assurance using a hybrid scanner.

With PET/CT, the CT scanner is coaxial with the PET set of detector rings.¹⁴ A clinical example is shown in Fig. 1. Again, photon attenuation values at 511 keV along a given ray may be determined more directly and quickly by CT than by use of an external positron source so as to make quantitative activity measurements more exact and more rapid. Such standard uptake values (SUVs) can be used to measure organ or tumor function and their variation with outside intervention such as chemo or radiation therapy. The SUV is defined as the percent injected activity per gram of target divided by the total body mass. Some authors have proposed using SUV magnitudes to make clinical assessments directly. Here one compares prior or possibly disease-specific SUV values to obtain a clinical result. This remains a research topic due to the difficulty of selecting the correct voxel(s) to determine the relevant standard uptake value.

III.A.5. Computers and software in nuclear medicine

It is important to realize that imaging and the subsequent kinetic analyses are strongly dependent upon decay event manipulation using processors within and outside the camera or PET scanner. Inside the camera or PET crystal configuration, the analog computation of Anger has been replaced by local microprocessors. These devices allow for uniformity correction, energy stability, and event relocalization. In uniformity applications, the edge packing of primitive cameras, due to multiple visible photon reflections at the crystal boundary, has been eliminated in the clinical image.

Reconstructions for 3D imagers depend upon software and its careful application to the limited set of projection data. Filtered back projection³¹ and ordered subset expectation maximization³² are limiting cases of several available algorithms. Using stored projection data, the imaging physicist can attempt reconstructions with multiple algorithms. In most of these, parameters may be adjusted during the reconstruction process to optimize one or another feature of the resultant cross sections of the patient. Optimal reconstruction for quantitative imaging continues to be a research topic.

III.B. Radionuclide therapy

As noted above, ¹³¹I is still used in therapy of thyroid malignancy and neuroendocrine tumors. Many clinical trials involving antibodies are being carried out. Their greatest success has occurred in therapy of B-cell lymphomas. This result is based on the greater sensitivity of B cells to a given radiation dose as compared with solid tumors such as colon or breast cancer. While no FDA-approved antibody therapies are available for solid tumors, two approved antibody-based agents are in current usage for B-cell lymphoma therapy. Bexxar³³ involves ¹³¹I and Zevalin³⁴ uses ⁹⁰Y as labels for their respective anti-CD20 antibodies. A crude whole-body dose is computed for Bexxar, while Zevalin requires no dose estimation during the treatment. Both therapies, generally under the purview of radiation oncologists, involve large amounts of cold (unlabeled) antibody to saturate unwanted antigen sites.

In order to enhance solid tumor radiation dose, one strategy is injection into the lesion's vascular bed. This circumvents using the IV route and puts essentially all the activity into a small volume. At present, there are two FDA-approved protocols for treatment of tumors in the liver by direct injection. Both procedures involve use of radioactive spheres to reduce effects of recirculation. Access to the site(s) is afforded by catheterization of the patient's hepatic artery. Glass or plastic spheres labeled with ^{90}Y are injected by the interventional radiologist under x-ray guidance. Targeting is previously proven using $^{99\text{m}}\text{Tc}$ albumin microspheres injected via the same route. Concern over possible lung radiation dose is taken into account by measuring, via gamma camera, the relative amount of the total activity going into the lung field. Very high estimated tumor doses are achievable; values exceeding 100 Gy (Ref. 35) have been cited. These liver protocols and associated dose estimates are currently being evaluated by an AAPM Task Group.

Nanotechnology continues to be of growing research interest for radiotherapy. The strategy is to generate moieties that will exit the bloodstream at tumor fenestrations and even pass into the cytoplasm (or nucleus) of the target cell. Specificity is to be obtained using attached antibodies or perhaps oligomers of DNA or RNA that are specific to a molecular target. For example, silencing pieces of RNA are a potential method to stop expression of oncogenes within the tumor. Stable 50 nm liposomes were a prototype for this technology that has expanded to include such diverse moieties as cyclodextran, carbon fibers, and gold particles. It is generally possible that both chemotherapeutics and/or beta or alpha sources may be incorporated into such structures. Activity may be loaded during production in the radio pharmacy or later via a chelator so that the label is at low risk for release into the body. A recent report by Rossin *et al.*³⁶ used 100 nm polystyrene latex beads and anti ICAM-1 antibody to target lung endothelium in rats. A ^{64}Cu label permitted imaging with a small animal PET system.

III.C. Absorbed dose estimation in imaging and therapy

III.C.1. General

Therapeutic applications require careful dose estimates. The traditional method to perform this calculation, developed by physicists at ORNL,³⁷ involves the separation of the geometry and emission properties of the radiative process from time-dependent effects as indicated in Eqs. (1) and (2). Clinical S matrix values are obtained by using Monte Carlo methods³⁸ on mathematical representations of human geometry. These values are in common use in estimating patient organ doses. A typical patient (or volunteer) radiation dose is computed by combining animal PK data and human phantom S values. Correction for the difference in anatomic size is done by a perfusion argument based on the fraction of total blood flow to the organ of interest. This is the type I computation outlined above.

III.C.2. Patient-specific (type II) dose estimates

Few patient-specific dose estimates are being done presently. In most clinical therapy cases, $A(t)$ values are obtained by geometric mean imaging and then integrated to find \tilde{A} for the patient. For reasons of simplicity, these results are used in conjunction with an S result obtained from a geometric phantom. Yet, as described previously, the S values for a phantom may not represent a particular patient. This discrepancy includes both organ sizes and their separations in space. Because of the possibly large difference between the masses of the target tissues, the inaccuracy of an estimate based on human phantom S values can be on the order of several fold in tissues like the liver or spleen.

Because of mass uncertainty, some organ doses are inherently very difficult to predict. Of primary importance is the red marrow (RM) dose. Marrow is often the organ that limits the total amount of injected activity as this tissue is very sensitive to radiation. Dose estimation has been developed by Siegel *et al.*³⁹ for blood-borne materials and generalized by Sgouros *et al.*⁴⁰ in separate AAPM Task Group reports. In conventional analyses, RM is assumed to have a standard mass and a time-activity curve proportional to that of the patient's blood. Both assumptions may be at fault. Of initial interest is the mass assumption since a given individual may show RM size variation. No method is yet apparent to estimate a patient's unknown RM mass. This may be considered an objective for intensive future investigation as this knowledge is important for various patient therapies—not just those generated with ionizing radiation.

IV. THE FUTURE OF NUCLEAR MEDICINE

IV.A. Imaging

Planar imaging will continue to play a role in clinical applications of nuclear technology. Whole body scanning of tumor-targeting agents will have extended application. Here the physician will use agents—such as bone seekers—that target to a single tissue so that tomographic considerations need not enter the diagnostic process.

It is apparent that hybrid imagers will become the standard of future nuclear tomographic studies. Associated with this modality will be organ-specific uptakes that will further enable improved dose estimation. Identification of the strong emitters seen in the planar sections via associated CT or MRI scans will probably lead to greatly increased clinical imaging throughput for these devices. Along with the hybrid philosophy would be a commensurate decrease in CT and other purely anatomic scans of the patient.

Some differences occur between the two aspects of hybrid imaging systems. The CT scan is typically a rapidly acquired image with breath holding by the patient. Any nuclear scan, due to low photon numbers, is necessarily slower and would therefore blur some organ motions such as liver and lungs. One would anticipate that future analysis would try to reduce this motion by use of physiological gating techniques akin to

those used in a MUGA scan. Alternatively, the CT scan could be acquired over several breathing cycles to better correspond to the PET or SPECT situation.

IV.B. Novel pharmaceutical development

Nuclear medicine has always been limited by the availability of specific tracers that can preferentially localize in tissues of interest. With recombinant methods, novel proteins, RNA, and DNA fragments will continue to be developed. Nanotechnology, initially defined using colloids and liposomes, will also be further enhanced with newer structures and novel methods of labeling. Combinations of these entities will become more common; e.g., nanoparticles with antibodies on their surface to effect more specific targeting.

Generally, new agents are initially tested in an animal model—usually a special mouse. Genetic modifications allow murine species to carry human genes for proteins of purely human interest such as carcinoembryonic antigen. This work will progress and allow more rapid engineering to find improved agents for both normal tissues and tumors. Small-scale PET scanners will become the ideal way to conduct such biodistribution studies in mice. No longer will multiple animals need to be sacrificed at each time point; instead, relatively few animals need be followed by PET scanning to obtain quantitative organ imaging. As noted in the clinical case, PET/CT miniature scanners will enable the uptake data to become more rigorous and eliminate all but a few well-counter evaluations. The latter will be required in those tissues that are not demonstrable on the tomographic image set. If PET labels are not possible in cases of slowly targeting tracers, use of miniature SPECT/CT scanning will become a suitable alternative method.

Numerical comparisons of agents will become more important because of the multiple engineering possibilities available to the biochemist and molecular biologist. By replacing single amino acids in a large protein, for example, enormous numbers of possible tracers may result. Yet clinical trials are expensive so that selection of the optimal agent is probably best done by comparing targeting in animal studies. Here the fundamental quantity is uptake measured in units of percent-injected dose per gram of tissue. Imaging and therapy figures of merit have been derived and can be expected to be used in such agent comparisons in the future.⁴¹

IV.C. Patient-specific nuclear medicine therapy

With improved targeting and imaging, a unique therapy may be possible for a given individual. This optimization should eventually encompass both unlabeled and radiolabeled pharmaceuticals. In the former case, it is unclear today if lesion targeting actually occurs with standard chemotherapeutic agents in a specific person. Eventually, an imaging study—probably using PET/CT techniques—with radiolabeling of the therapeutic material will be used to prove efficacy. If it can be shown via such imaging that a given chemical agent does not demonstrate significant localization at the disease site(s), other therapeutics could be selected *a priori*. The

result would be a lowering of the incidence of toxicity without associated therapeutic benefit. Physicists will play a fundamental role in these analyses. The same situation would hold for radioactive agents that effect radiotherapy. Imaging with small amounts of activity could be used to test for patient targeting.

A single agent may not continue to be appropriate throughout the history of the disease since earlier treatments may have selectively destroyed those tumor clones that were once targeted. Thus, before any treatment prescription is written, an imaging investigation should be conducted to determine if the lesion(s) are still positive for the original antigen or tumor marker. With time, a battery of possible chemo- and radiosequences should evolve out of this strategy. There is a growing interest in combination therapies whereby both chemotherapeutic and radiotherapeutic moieties are used in conjunction. Thus, physics input into the chemotherapy realm will have important applications in that field as well as in radiation therapy.

Changes in the method of dose estimation are anticipated. Equation (1) is a simplification of the actual physical situation. It contains the implicit assumption that separation of geometric (S) and temporal effects (\bar{A}) is possible. Yet if the mass of the target tissue is changing during the course of the therapy, S becomes a function of time. In that case, the radiation effect is better computed as an organ rate quantity dD/dt (cGy/h),

$$dD/dt = S(t) * A(t), \quad (3)$$

where the target organ mass variation must be provided by the observer using anatomic imaging such as CT or MRI. Such mass effects have recently occurred in lesions seen in clinical trials of antibody-based lymphoma therapy. Here, because of the radiation sensitivity of the tumor type, target sizes were being reduced while the radioactivity was still present.⁴² Thus, future radiation therapy trials using radionuclides will need to consider dose rate rather than only the final dose. Integration will then be done over time intervals to obtain a final result in cGy. An optimal amount of activity would be selected by the physicist with knowledge of normal organ toxicity.⁴³

Among the physicist's new responsibilities would be the summation of ionizing radiation doses from external beam therapies as well as the internal emitters. Treatment planning is going to become a more sophisticated physics business with a result for each treatment as well as ongoing total organ dose tabulation. Comparison of the effectiveness (quality factor) of internal emitters, particularly alphas and also betas, with external beam photon doses would be one outcome of such work. In addition, such tabulations will enable the oncologist to evaluate the incidence of untoward effects due to radiation dose in long-term survivors.

Nuclear medicine physicists will have an additional responsibility in therapy planning. In addition to total organ doses, it is anticipated that voxel-based treatment plans will be developed. Initially, these will involve the tumor site(s) but will evolve to include normal tissues that have differen-

tial sensitivities; e.g., the kidneys. Dose-volume histograms, comparable to results seen in external beam therapy, would be generated using an imaging agent. Technical problems are anticipated in following a given spatial volume or organ segment over time. Hybrid scanning may be of use in this objective—however, very specific molecular targeting may obviate this problem

V. CONCLUSIONS

Because of the need for functional counting or imaging, nuclear methods will always be part of clinical evaluations. A nuclear probe is essential to the endocrine service for thyroid examination. Other specialties such as cardiology would continue to use planar gamma cameras to determine myocardial infarct locations and the LVEF of the patient. Internists may need to find an occult bleed or transit times for intestinal segments. No other present technology lends itself to such evaluations.

In an era of organ transplantation and prosthesis implantation, functional performance evaluations will increase in the future. However, their application may become even more restricted to the relevant medical service. If the pancreatic islet cells are implanted, for example, it would seem logical that endocrine service would want to follow their function or associated changes in stomach transit times of the diabetic patient being treated. Bone scans of knee or hip replacements could easily become integral to the orthopedic surgeons practice—and not be referred to the nuclear radiologist. Surgeons will continue to exploit use of probes in the OR to determine sentinel node location and to find the stage of the patient's cancer. Status of the renal or hepatic transplant could also be followed by small cameras in the surgical suite.

A second reason for continuing nuclear medical applications is the specificity of the targeting. Nuclear detector sensitivity allows, in principle, location of single molecules within the patient. This possibility has led some to rename the field molecular imaging and therapy. Enormous efforts are currently going on to develop radiopharmaceuticals to allow such specific and sensitive imaging in a clinical context. Small-scale cameras—particularly of the PET type—will expedite development of the RP that is specific to the molecule of interest.

From novel RPs, one can visualize growth of patient-specific radiotherapy. Nuclear technology has had too little application to disseminated malignant disease. An advantage that nuclear methods have is that targeting can be proven prior to beginning treatment. If the accuracy of the uptake measurement can be improved; e.g., via hybrid imaging to $\pm 5\%$ instead of the current $\pm 30\%$, treatment planning may proceed in radiation oncology practices. While presently used only in hepatic and lymphoma therapies, future applications should expand to various solid tumors—and metastatic sites. Physicists will become more important in such treatment plans and in predicting associated absorbed doses. One can imagine, however, that diagnostic radiologists may have little direct involvement. Radiation oncology may

mimic a strategy seen in other specialties such that practitioners will purchase imaging equipment necessary to define disease and its treatment course so as to make consultation with their imaging colleagues unnecessary.

Back in the imaging department, nuclear technology is increasingly being incorporated into a CT or MRI system. With the advent of hybrid imagers, the nuclear medicine practitioner is faced with the prospect of purely nuclear imaging vanishing as a separate radiological specialty. Much like the smile of the Cheshire Cat from *Alice in Wonderland*, the only vestige left may become the activity seen in such fused images. PET as a separate modality has evaporated and been replaced by PET/CT. SPECT is in similar danger. Associated with hybridization of imagers is a necessary retraining of typical radiologists. They will now have to expand their expertise areas to include RP targeting and its physiological significance. Rigorous lines of separation are in the process of being removed and a better imaging generalist produced.

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