Nuclear Medicine in the New Millennium

INTRODUCTION

Although many individuals in our field are qualified to predict the future of nuclear medicine, two came immediately to mind while I was contemplating such an editorial for this issue. Instead of choosing between them, I thought it fitting to have them coauthor the following piece. This linking of a basic science researcher with a nuclear medicine physician (who is also a clinical science investigator) is precisely where a great deal of our future lies—in such individuals working more closely together to discover and perfect techniques that advance diagnosis and therapy.

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The discipline of nuclear medicine is on the verge of rapid growth as it establishes its role as an imaging technique of the emerging molecular diagnostics and therapeutics coming from the merger of medicine and biology. Revolutionary advances have occurred in biologic research and clinical medicine during the last decade. These advances are creating new opportunities for research and clinical activities in nuclear medicine. Nuclear medicine is responding by expanding the biologic aspects of its research programs, as well as its diagnostic and therapeutic procedures. The therapeutic applications of nuclear medicine are an important part of the practice of the specialty and are showing clinical efficacy in several areas such as treatment of bone pain from metastatic cancer, neuroblastoma, and recurrent low-grade B-cell lymphomas. This editorial will focus on the diagnostic aspects of nuclear medicine as we proceed into the new millennium.

Diagnostic nuclear medicine is based on several fundamental principles:

1. The development and use of radiolabeled molecules to image or measure the molecular basis of disease for early detection, accurate characterization, treatment planning, and assessment of therapeutic outcomes.
2. The design and development of radionuclide imaging and measurement devices for performing molecular examinations of patients.
3. The use of the tracer technique to perform these procedures with minimal or no mass effects that could alter the biologic process that is being imaged or measured.
4. The ability to measure molecular concentrations and rates of biologic processes involving substrate concentrations down to micromoles to femtomoles per gram of tissue.

IMAGING SYSTEMS

Imaging systems in nuclear medicine are going through a period of rapid technology development led by, but not restricted to, PET. Both the academic and the industrial sectors are increasing their efforts in the development of new detector materials, high-speed digital electronics, image reconstruction algorithms, and computational systems. Although lead collimators restrict improvements in single-photon imaging because detection efficiency decreases by the square of resolution improvement, coincidence imaging still has much room for improvement. The 2-dimensional fanbeam geometry of coincidence detection is being replaced with 3-dimensional cone-beam detection and reconstruction that will increase efficiency by 3- to 4-fold. Because image quality and spatial resolution are limited by the number of counts obtained, this change will allow significant improvements.

Research in image reconstruction algorithms is shifting image reconstruction from conventional convolution approaches to algebraic, iterative algorithms for several reasons. First, the algebraic algorithms provide for the use of statistical criteria, such as maximum likelihood, to optimize image reconstruction in terms of the limiting factor of counting statistics and system noise. Within the statistical limitations of nuclear medicine images, the use of algebraic algorithms can produce reductions in image noise by approximately a factor of 2. Second, algebraic algorithms allow the incorporation of a priori information into the reconstruction process to further improve image quality and spatial resolution. For example, these algorithms allow the incorporation of such factors as attenuation correction, anatomic information, detector normalization, angulation error in coincidence detection, detector response functions, and positron range to reduce noise and some of the resolution loss that results from these factors. The use of a priori information can be

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expected to reduce noise by a factor of 50%–100% and improve resolution by 30%–40%. These algorithms are best suited to accommodate time-of-flight localization of positron-labeled tracers, if advances in detector technology allow collection of this information. This would further improve image quality. Optimization of the estimates of biologic parameters can also be incorporated into the image reconstruction process. These algorithms do come with a large computational burden. Fortunately, the electronic information era continues to increase computational speed at reduced costs, with a doubling of speed and halving of costs every 2–3 y. New computational technologies that could produce increases by powers of 10 at low costs are also being developed. Thus, computation will not be a limiting factor over time.

Not only are mergers within academic disciplines and between industries occurring, but technologies such as PET and SPECT, PET and CT, and PET and MRI are also being merged into single devices. PET/SPECT devices allow nuclear medicine clinics to initiate clinical PET services using both PET and SPECT income to finance their entry and to combine SPECT and PET procedures in the same patient. For example, a SPECT cardiac perfusion study can be combined with the PET measure of glucose metabolism. The PET/CT device is being driven by the desire for CT scans that show the anatomic location of disease more accurately for planning surgery, radiation, and biopsies, fused with the molecular images of PET for the most accurate detection and characterization of the biologic nature of disease. In addition, CT provides a fast and accurate means to perform attenuation correction for PET. Providing images with anatomic detail will also improve the acceptance and confidence in nuclear medicine imaging of referring physicians and provide opportunities that will be thought of only when this new technology concept is put into use. Combined PET/CT is a very important development in nuclear medicine, as is the development of SPECT/CT devices.

PET RADIOPHARMACIES

A major innovation has occurred in the development of "electronic generators" for PET. Self-shielded, miniaturized cyclotrons and automated chemical synthesis devices have been integrated into a system concept under the control of a personal computer. These devices are providing FDG to nuclear medicine imaging facilities to meet the practical requirements of a clinical service. The unit operation concept of the automated chemical synthesis device, such as solvent and reagent addition, column separation, and others, is similar to DNA and peptide synthesizers and combinatorial chemistry devices of drug discovery and can be expected to benefit from these technologies. Automated chemical synthesis devices provide a flexible platform to reconfigure the unit operations for the synthesis of new radiopharmaceuticals developed for clinical services. These electronic generators have high fixed and low variable costs that can be expected to provide radiopharmaceuticals in volume that can respond to cost pressures. Linear accelerators are also being developed as a base technology to provide the radionuclides for use with automated synthesis devices.

MOLECULAR IMAGING PROBES

The development of molecular imaging probes is the key to the importance and growth of nuclear medicine in the new era of molecular medicine, which is occurring by the merger of medicine and biology. Molecular medicine is redefining the research and clinical questions to be addressed as research progresses into the discovery of the molecular mechanisms and errors of disease and the development of new molecular treatments.

Where will the new molecular imaging probes of nuclear medicine come from to meet the needs of molecular medicine? The approach of biochemists causes them to reduce the complexity of a biologic process into its components and then develop assays for the components of interest. This approach yields simplified assays that have produced and will continue to produce probes that can potentially satisfy the restrictions placed on in vivo nuclear medicine imaging procedures. The principle of pharmaceutical design focuses on creating a small molecule that will interact with a single target and modify its function. Although the biochemist typically works in the in vitro setting, the pharmaceutical scientist shares with nuclear medicine the systemic delivery of a molecule directed at a target in vivo. In the case of the pharmaceutical, the molecule is given in mass amounts to modify the function of the target, whereas in nuclear medicine, the molecule is given in nearly massless amounts to image and measure the function of the target.

The desired properties of molecules as pharmaceuticals and molecular imaging probes are very similar, with a few notable exceptions. In both cases, the molecule should (a) have high affinity for the target and low affinity for other molecular constitutes throughout the body to reduce side effects in the case of a drug or to reduce background in the case of the imaging probe, (b) be small and have sufficient lipophilic properties or carrier-mediated means to rapidly cross membranes to access the target, and (c) degrade minimally or slowly. The differences include the desire for the drug to clear the plasma and nonspecific tissue sites with half-times of hours to days, whereas, in the case of the imaging probe, the desired clearance is minutes to hours. In addition, the target-to-background ratio can be <1 for a drug, whereas with the imaging probe it must be >1.

The pharmaceutical sciences and industry are going through revolutionary times. The rapid growth in genetics and biology has focused on identifying the fundamental molecular nature of disease, and pharmaceutical scientists have developed automated chemical synthesis technologies, such as combinatorial and parallel processing schemes, for rapid production of tens of thousands of new candidate drug molecules and high-throughput screening of them to tens of molecules with desired properties. Nuclear medicine should take advantage of this development by produc-

ing new molecular imaging probes as labeled versions of these drugs, analogs of the drugs, or byproducts of this process that retain the favorable pharmacokinetic properties yet optimize them for imaging. This marriage of disciplines will also help focus the development of nuclear medicine imaging probes on the disease targets coming out of molecular medicine.

PARTNERSHIPS

Nuclear medicine should not only strengthen its relationship with biochemistry, molecular biology, pharmacology, pharmaceutical sciences, and industry for the reasons discussed above but should also link molecular imaging diagnostics with molecular therapies. This intersection can be synergistic at the discovery level and in clinical care. At the discovery level, the pharmaceutical sciences can aid nuclear medicine in molecular design, and nuclear medicine can aid the pharmaceutical discovery and approval process in several ways:

1. Provide the means to titrate the drug to its site of action within an organ system in vivo;
2. Assess the pharmacokinetics and pharmacodynamics of the drug; and
3. Determine whether the biologic disease process has been properly modified by the drug.

All these things can be performed in animal models of disease and patients on the basis of a commonality of in vivo imaging procedures used. This approach to the pharmaceutical development process will also provide the knowledge base and procedures for linking molecular imaging diagnoses with the selection and evaluation of molecular therapies in clinical practice.

Nuclear medicine will build a new research paradigm of in vivo integrative mammalian biology of disease with the biologist, pharmacologist, and pharmaceutical scientist. Basic biologic scientists are not comfortable in the clinical environment. They have selected the mouse for producing genetically engineered disease and human cell line mammalian models of disease. Nonprofit and commercial organizations produced approximately 2 million mice in 1999 that are genetically engineered for various human diseases. This number is predicted to increase 3-fold over the next 3 y, with the increases coming mainly from companies that produce these mice for research. The biologist faces a difficulty in the lack of efficient biologic assay techniques for in vivo studies of these new animal models to understand the mechanistic alterations of disease and to guide and evaluate molecular therapies. Nuclear medicine can create a great opportunity to strengthen its fundamental science through such programs. At the same time, nuclear medicine can provide an important solution for the biologic and pharmaceutical scientists by developing in vivo molecular imaging at the level of the mouse with assays familiar to and important to them. The development of technologies such as microPET will make this happen, as will the continued transformation of in vitro molecular assays from basic biology to in vivo molecular imaging assays, such as those for accessing gene expression, signal transduction of cell communication, and enzymology of substrate metabolism and synthesis.

EDUCATION

Research builds new directions for a discipline, but educational programs incorporate discoveries into the discipline for its longevity. The number of nuclear medicine training programs and residents being trained in them has been decreasing over the last decade. The research coming from molecular imaging with PET and SPECT provides the opportunity for and necessitates reinvigoration and redesign of nuclear medicine training programs.

Nuclear medicine has established a training and practice relationship with radiology on the basis of a common ground of imaging and has less well-developed relationships with internal medicine. Recently, the American Board of Nuclear Medicine (ABNM) and the American Board of Internal Medicine (ABIM) have instituted a joint training program much like that ABNM has with the American Board of Radiology. These joint programs allow nuclear medicine to engage both the imaging community of radiology and the practitioners of internal medicine.

As molecular medicine evolves from the merger of biology and medicine, nuclear medicine can play a major role in this evolution by merging with biology and medicine to become the imaging technique of molecular medicine. New training programs will produce new generations of physicians trained in the subspecialties of medicine and nuclear medicine and of nuclear medicine and radiology. The question arises as to where these new generations of nuclear medicine physicians will practice. The best answer to this question is just to go forward boldly and make it happen. The principles on which these changes are based are sound and are in the direction in which all of medicine is headed. The development of new training programs does, however, require courage and commitment to move into the unknowns of the future with an open mind and a desire to do something that has not been done before. It is this free spirit and the merger of disciplines that created biochemistry, molecular biology, microcircuit technology, the personal computer, and the information technology of today and is now creating the molecular medicine of tomorrow. As Alan Kay, of Macintosh fame, once said, "The best way to predict the future is to invent it."

Over the short term, the educational process can be aided in several ways.

1. The new ABNM/ABIM joint training programs can rapidly be implemented into existing nuclear medicine training programs. This will help merge nuclear medicine and internal medicine, help nuclear medicine evolve as a part of the evolving medical practice, produce advocates for the use of nuclear medicine procedures within medical practices, and, most important, produce succes-

sive generations of nuclear medicine physicians who represent the knowledge and expertise of both disciplines.

2. Training programs with radiology can be continued and improved. Radiology is also going through many dramatic changes, such as the joining of interventional radiologists, surgeons, and interventional cardiologists to perform certain procedures. Nuclear medicine and radiology should take a fresh, progressive, and aggressive look at how to modernize their relationship. The PET/CT device provides a technology-based pathway, but novel ways to be good partners in research, clinical service, and education that will be of value to each partner should be explored.
3. Some university-based nuclear medicine training programs can start MD/PhD training programs in which some individuals would be accepted into both the residency and a PhD program. This will involve physicians who have made a commitment to nuclear medicine and will then be trained as physician scientists. These MD/PhD programs can be built on and will strengthen relationships with disciplines such as pharmacology, biology, genetics, biochemistry, chemistry, physics, and engineering. The goal for these programs is to produce new leaders for a changing academic discipline of nuclear medicine. Such a program has been initiated at UCLA. Funding will come from National Institutes of Health training and research grants, practice, and hospital funds. These programs will complement and enrich nuclear medicine clinical training and joint training programs with radiology and internal medicine.
4. More nuclear medicine in its role of imaging the molecular basis of disease can be incorporated into medical student education. Advances in modern biology and the evolution of molecular medicine are creating interest and moving medical education in this direction. We should seize this opportunity. Our imaging technologies can allow students to see the biologic basis of disease, the interaction of drugs with disease processes, and the therapeutic modification of the biologic nature of disease.

New nuclear medicine physicians that are so trained will be part of the expansion of nuclear medicine as an independent academic discipline and service integrated with radiology and with medicine. The future of nuclear medicine will fundamentally strengthen and expand by its relationship with the biologic and physical sciences. Newly trained nuclear medicine physicians will go into practices that are solely nuclear medicine; are part of a radiology practice; and are part of internal medicine–based practices in oncology, cardiology, neurology, general internal medicine, and surgery. Medicine is changing, and more medical practice groups are incorporating imaging into their practices. If we respond appropriately with leadership, we can provide the professional home for these new configurations.

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