Physics Applications in Nuclear Medicine: Carpe Photon

The year 2006 brought some fascinating advances in physics applications in nuclear medicine. Significant advances were seen in detector development and image analysis methods, and new tools and information for dosimetry became available. Another in the series of radiopharmaceutical dosimetry symposia was held, with proceedings to be published soon. Electronic resources continued to play a significant role in these areas of specialization.

Instrumentation and Analysis Innovations

The annual meeting of the SNM included a number of hardware and software innovations and tests thereof that are likely to improve the quality of clinical and research practice. As technology has improved, some important, previously discarded concepts have re-emerged. Prominent among these is time-of-flight (TOF) PET. The motivation for this re-emergence is demonstrable improvements in resolving small structures, as pointed out by Simon Cherry (*1*). One group, for example, discussed results from whole-body imaging of obese patients (*2*). Improvements in photomultiplier tubes (PMTs) and in lutetium oxyorthosilicate (LSO) crystal material are under continued development by researchers and members of industry (*3*). Increases in the size of circular geometries or the separations of box-type geometry detectors to accommodate different size subjects and organs require good depth of interaction (DOI) correction. Some approaches that are being evaluated include Phoswich multicrystal scintillator ensembles looked at by one or more PMTs (*4*), avalanche photodiodes (APDs) assigning depth in a crystal between opposed APDs (*5*), the use of high-purity germanium semiconductor strip detectors (*6*), and physically stacked semiconductors (*7*). Novel solutions include signal processing of multilevel ensembles of scintillators in which reflectors produce signal wave forms that permit 3D crystal assignment. Brain images were provided for 4 layers of gadolinium orthosilicate (GSO) crystals (*8*) in a system that has been extended to 8-layer DOI encoding (*9*). The NanoSpect (Bioscan, Inc.) multipinhole aperture class of systems is showing impressive results leading toward high spatial and temporal resolution imaging of dynamic processes (*10*). Increasing use of simulation and modeling tools in the design of PET and SPECT systems has been aided greatly by the efforts of the GATE group, working with the GEANT4 collaboration. This was the topic of many presentations at this year's IEEE Medical Imaging Conference. The versatility of this tool set has been extended beyond detector design and evaluation to many areas, including radiation dosimetry (macro- and microscopic) and radiobiology modeling (*11*).

Because they are unaffected by strong magnetic fields, APDs are now appearing in PET/MR animal imaging systems and will soon be employed in commercial clinical MR imaging devices (*12*). In view of the important role of CT units coupled to nuclear imaging devices, PET/MR imaging is likely to have a major impact on clinical imaging. Interest continues in coupling new position-sensitive and multianode PMTs to new crystals, arrayed in novel modular geometries. The group at the Jefferson Laboratory continues to pioneer these developments (*13*). The use of the cerium-doped halide scintillator $LaBr_3$ with this new generation of devices appears promising, as the size and quality of the available material continue to improve (*14*).

A major roadblock that has slowed the full development of PET is the difficulty of gaining access to tracers other than ^{18}F-FDG. At the June meeting of the SNM, Ronald Nutt, PhD, reviewed the history of the development of clinical PET from his industrial perspective. He envisioned the impact of the next generation of silicon-based radiopharmaceutical synthesizers dedicated to the production of a single amount of a specific ^{11}C- or ^{18}F-based radiopharmaceutical. The process would be U.S. Food and Drug Administration (FDA) approved, with a wide range of useful compounds available for patient care and research. Furthermore, the amounts needed for each dose would be small, which would make it feasible to produce the needed amount of radionuclide with a small, low-cost cyclotron, which could then be located in all/most major nuclear medicine programs. Because it is currently so difficult to get most radionuclides, the realization of this projected future will be most welcome.

Correction techniques for partial volume, scatter, attenuation, and collimator penetration degradations continue to receive extensive attention. Simulation studies have provided important insights, and corrections are included by different manufacturers in the increasingly sophisticated software packages now being offered with new systems. Many nuclear medicine scientists have contributed the essential insights and methods for coping with the signal processing and image reconstruction challenges. Much of this work is chronicled in the *IEEE Transactions on Nuclear Science*.

With the emergence of new tools, the challenge becomes how to best choose which tools to use for what purpose. At least 2 types of instruments and uses are included in this challenge: those that produce a broad view and those that facilitate a focus on small regions of interest. New systems are emerging in which sequential decisions within the imaging session can greatly influence the

outcome. Many instruments can be used in both ways. After surveying the patient, one can go back and rescan a suspect area with a change in sensitivity/resolution, imaging angle, or dwell time. New systems promise additional flexibility. A "D-SPECT" system, demonstrated at the 2006 SNM Annual Meeting in San Diego, CA, uses 8 cadmium zinc telluride detectors, each of which is directed at the region of interest. This is typically the heart but could just as easily be a suspect tumor site. New ideas are emerging in which one is given the option of dynamically opening and closing apertures in pinhole collimators so as to achieve desired resolution in selected spatial regions (*15*). Focal lengths could also be changed by moving the plates with respect to the imaging planes. As these options continue to emerge, physicians and technologists will increasingly need technologies and techniques that allow them to interact with procedures in near real time if the desired benefits are to be fully realized.

Radiation Dosimetry and Radiobiology

Good dose estimates are always needed for new and existing diagnostic agents and are essential to gain FDA approval, allow use in research institutions and medical centers, and support other applications. In these uses, average dose estimates based on standardized models of reference adults are sufficient for the task. Standardized dose estimates for a vast array of the important radiopharmaceuticals in use today have been and continue to be published by the Task Group on Dose to Patients from Radiopharmaceuticals of the International Commission on Radiological Protection (ICRP) (*16*). Much of this information is routinely available on the RADAR Web site (see below) or in more complete form as published documents from the ICRP. The group plans to combine data from all of their previous and upcoming dose estimates on a searchable CD during 2007.

Radiation dosimetry for positron-emitting tracers continues to be of interest, with the continuing expansion of PET systems and techniques. Radiation dose estimates were presented for a number of new compounds, including a dopamine D1 receptor radioligand (^{11}C-NNC 112) (*17*), ^{11}C-labeled raclopride (*18*), and ^{18}F-galacto-RGD (*19*), which is a potential radiotracer for imaging of vß3 expression.

It is nearly time to forget the use of "stylized" phantoms for standardized dosimetry. The models of adults (*20*), children (*21*), and pregnant women (*22*) that have served us well for 3 decades will soon be completely replaced by a new series of realistic, image-based models, ultimately derived from human image data. New models of the adult male and female have been developed from images of individual subjects by the group at the Forschungszentrum für Umwelt und Gesundheit (GSF) in Germany (*23*). These models and models of pediatric and pregnant female subjects based on nonuniform rational B-splines (NURBS) will be implemented in the next release of the OLINDA/EXM dose assessment software (*24,25*). Stabin et al. (*26*) showed that microimaging systems can be used similarly to produce more realistic animal models for dose calculations, when dose estimates for the animals themselves may be of concern.

The most important applications of radiation dosimetry, however, continue to be in radiation therapy. Ferrari et al. (*27*) provided a dosimetric model for the study of the treatment of brain tumors with ^{90}Y-DOTATOC. Breitz et al. (*28*) provided a comprehensive report on the dosimetry of ^{166}Ho-DOTMP, a very promising agent for skeletal targeted radiotherapy but one with a future that is currently in doubt as a result of stalled clinical trials. Hänscheid et al. (*29*) noted the importance of the use of patient-specific parameters in the treatment of thyroid cancer in an international, multicenter study. A beautiful continuing education article was prepared by Cremonesi and colleagues on the use of dosimetry in peptide radionuclide receptor therapy (*30*). Kontogeorgakos et al. (*31*) provided a study of the use of patient-specific dose calculations in therapy with ^{111}In-DTPA-D-Phe1-octreotide (*31*). Song et al. (*32*) presented a method for patient-specific dose assessment for patients in radioiodine therapy who present diffuse lung metastases.

Ameliorating the possible harmful effects of radiation on normal tissues via intervention may be an important component of successful therapy with radiopharmaceuticals. Förster and colleagues (*33*) provided results from animal studies focused on the use of a single-chain antibody and streptavidin construct with the use of radiolabeled DOTA-biotin to attempt to reduce renal dose during such therapies. Vegt et al. (*34*) showed that renal uptake of radiolabeled octreotide may be inhibited by succinylated gelatin in human subjects, thus reducing radiation dose. (Note: a follow-up discussion of this article appeared in an October letter to the editor and response [*35,36*]).

As noted in this space 2 years ago, a follow-up to the 30-year running Oak Ridge (and, in 2002, Nashville), TN, radiopharmaceutical dosimetry symposium series took form in the 1st International Symposium on Radionuclide Therapy and Radiopharmaceutical Dosimetry. This meeting was held in conjunction with the annual European Association of Nuclear Medicine (EANM) congress in Helsinki, Finland, in September 2004. The 2nd international symposium was held in 2006 in conjunction with the annual EANM congress in Athens, Greece. Sessions were held on dose planning in radionuclide therapy, dosimetry and radiobiology, combining external beam/radionuclide therapy, data collection methods, individual practice of the use of a number of agents, peptides, applications of radioimmunotherapy, therapy for thyroid cancer and bone pain palliation, and other important topics. The proceedings of the meeting should be published in 2007 in *Cancer Biotherapy and Radiopharmaceuticals*, the journal in which the 2004 proceedings appeared.

An international consensus continues to grow around the concept that patients given radiopharmaceuticals for

therapy deserve the same individualized attention and optimization of their radiation therapy as do patients treated with external sources of radiation, which has been undergoing constant improvement for decades. The 1997 Euratom Directive (*37*) mandated the use of patient-individualized therapy planning for radiopharmaceuticals, and current practice in Europe is increasingly reflecting this impetus. Our European colleagues are clearly in the lead in the rapidly advancing field of patient-individualized dosimetry, as evidenced by their numerous contributions to literature and their recent work on international dosimetry symposia. Those in the United States hopefully will be following this lead in the near future, both in science and legislation, but they obviously will be playing catch-up for some years to come.

Our traditional concepts of the use of average absorbed dose to a whole organ or tumor to predict radiation effects continues to be challenged by new evidence that a number of processes taking place at the cellular and subcellular level, including the "bystander effect," are clearly important to the end result of the irradiation of biological systems. Boyd et al. (*38*) compared the induction of such bystander effects by external-beam photon radiation with effects from exposure to ^{131}I-MIBG, ^{123}I-MIBG, and ^{211}At-MABG and found that "Potent toxins are generated specifically by cells that concentrate radiohalogenated MIBG. These may be LET [linear energy transfer] dependent and distinct from those elicited by conventional radiotherapy." Kishikawa et al. (*39*) presented some truly startling results that showed a marked difference in the bystander effect in an in vivo animal model, depending on whether the effect was delivered by ^{123}I or ^{125}I Auger electrons. The researchers lethally irradiated human adenocarcinoma cells with these nuclides, mixed them with unirradiated cells, and injected them in the anterior flank of nude mice. They found an "inhibitory" bystander effect with the ^{125}I system but a "stimulatory" bystander effect with the ^{123}I system (i.e., greater cell growth than in controls), from which they concluded that "These findings call for the re-evaluation of current dosimetric approaches for the estimation of dose–response relationships in individuals after radiopharmaceutical administration . . . ." Carlsson et al. (*40*) showed that the dose rates and exposure times needed to kill tumor cells with low-dose-rate beta irradiation must be carefully chosen to effect complete cell killing.

A few other items of interest:

- Madsen and colleagues (*41*) used a theoretical model to show how combined therapy (specifically with ^{131}I-MIBG and ^{90}Y-DOTATOC) in neuroendocrine tumors could possibly increase tumor dose.
- Uusijärvi et al. (*42*) gave an interesting overview of the use of proposed electron- and positron-emitting radiolanthanides for therapy applications.
- Neti and Howell (*43*) showed that cellular activity may show a log normal distribution of uptake and that this can have a substantial impact on modeling the biologic response of cell populations.
- A model was presented by Pandit-Taskar et al. (*44*) for organ and fetal dose calculations in ^{99m}Tc-sulfur colloid lymphoscintigraphy and sentinel node localization in breast cancer patients.
- Elgqvist and colleagues (*45*) explained relations between radiation dose from alpha emitters and growth of NIH:OVCAR-3 cells in mice.
- A review of the topic of radiologic and nuclear terrorism was given by Barnett et al. (*46*).
- Travis and Stabin (*47*) explored some possible dose and risk consequences for young females who received ^{131}I ablation treatment after the Chernobyl accident.

Electronic Resources

Electronic resources are rapidly replacing their paper-based counterparts, which were of course the only resources available for many years. The RAdiation Dose Assessment Resource (RADAR) Web site (www.doseinfo-radar.com) continued to receive heavy traffic for the free dissemination of standardized dose estimates, decay data, absorbed fractions, dose conversion factors, information on radiobiology and dosimetry literature, and other material. Many other Web sites with highly useful information, too numerous to describe in detail, can be found at the SNM links page (http://interactive.snm.org/index.cfm?PageID=944) or the University of Michigan health physics resource page (www.umich.edu/~radinfo/).

The OLINDA/EXM software continues to be distributed by the RADAR group (*48*), with its technical basis previously established in the literature (*24*). Vanderbilt University continues distribution of the code since receiving FDA approval through a 510(K) mechanism in 2004. An incremental update of the code is planned for 2007, and a major revision, including the realistic phantom series discussed previously, is planned for late 2007 or 2008. The update will also attempt to include realistic phantoms developed by others, as these are made available to the authors for inclusion. As noted previously, the ICRP Task Group on Dose to Patients from Radiopharmaceuticals hopes to move its dissemination of standardized dose estimates for adults and children for many dozen radiopharmaceuticals to an electronic format in the coming year.

A number of interesting e-mail lists (NucMed, RadPharm, PET-mail, Medical Imaging [Archive-Comm-L], Radsafe, Dose-Net, and others) exist for exchanging information actively with other interested parties daily by e-mail. Subscriptions are free, and digest versions (once per day summaries of all posts) are usually available. A large number of Yahoo groups (too numerous to mention) also focus on radiation and nuclear medicine physics issues and use a bulletin-board approach to exchange information. A Health Physics Society link (http://hps.org/resources.html) provides additional details.

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