plaques. Until recently, only advanced disease could be detected noninvasively. Nahrendorf et al. (*6*) described a combined PET/MR/optical nanoprobe to image the biomarker CD68 on macrophages in atherosclerotic plaques. Sanz and Fayad (*7*) described many of the novel targets being investigated for early detection of coronary artery disease by PET, SPECT, optical, and MR imaging.

Although ^{18}F-FDG in PET has been the gold standard for molecular imaging since the 1970s, there is always more to learn about this tracer. A recent essay by Hsu and Sabatini (*8*) discussed the Warburg effect of aerobic glycolysis and the fact that, although it is the key metabolic hallmark of cancer, we still do not fully understand its significance. In the 1920s, Otto Warburg discovered that, even in the presence of ample oxygen, cancer cells prefer to metabolize glucose by glycolysis, despite the fact that (compared with oxidative phosphorylation) this is a less efficient pathway for producing adenosine triphosphate (*9*). The Warburg effect is exploited for imaging tumors with ^{18}F-FDG PET, but do we ever wonder about the underlying mechanisms of why FDG is giving us either a high or low standardized uptake value in a particular tumor? Hsu and Sabatini remind us that the Warburg effect in tumor, as measured by FDG, may be telling us that genetic changes or perhaps demands of the microenvironment are driving the tumors to take up our favorite molecular imaging tracer. Why are some tumors refractory to imaging by ^{18}F-FDG PET? Many hypotheses have posited answers to this question, and it is hoped that by probing even deeper into tumor metabolism we can learn more about a particular tumor than just its mere presence or whether it is responding to a specific therapy.

Finally, let us not forget that the Nobel Prize in Chemistry was presented to Osamu Shimomura, PhD (Marine Biology Laboratory; Woods Hole, MA), Martin Chalfie, PhD (Columbia University; New York, NY), and Roger Tsien, PhD (University of California, San Diego) for the discovery and development of green fluorescent protein (GFP). Using GFP and the kaleidoscope of other proteins developed by Tsien, molecular imaging scientists have been able to study proteins, tracking the growth and fate of a variety of cell types to learn more about all the diseases discussed here. The winning topic of the 2008 Nobel Prize in Chemistry reminds us of the great science and scientists behind a ubiquitous tool in molecular imaging. As our arsenal of multimodality imaging instrumentation and probes grows, we will be probing ever deeper into the basic processes of metabolism, disease, and optimal health.

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Physics Applications in Nuclear Medicine: 2008 in Review

In 2008 many new ideas became available for internal dose assessment, and excellent progress was seen as well in the area of instrumentation. Significant advances were seen in detector development and image analysis methods, and new tools and information for dosimetry became available. Electronic resources continued to play a significant role in these essential areas of investigation.

Radiation Dose Assessment

RAdiation Dose Assessment Resource (RADAR) task group and Web site: The RADAR task group of the SNM maintains an information Web site (www.doseinfo-radar.com) that regularly provides dose calculational tools and data to SNM members and other investigators around the world, averaging 5,000 visitors with more than 30,000 page hits per month.

The focus of the RADAR task group is to: (1) provide accurate and up-to-date information on input data (radionuclide decay data, absorbed fractions, standard organ masses, and other data) needed for radiation dosimetry to the scientific community on a timely basis; (2) perform research and develop new models and techniques to improve the state of the art in internal and external dosimetry; (3) publish information on dosimetry models and methods in journal articles, books, book chapters, conference proceedings, and others; (4) develop and publish software tools that facilitate

calculation of standardized internal dose calculations; and (5) assess and disseminate standardized dose estimates for new radiopharmaceuticals.

The group is finishing the calculation of absorbed fractions and dose factors for the new generation of realistic phantoms (Fig. 1) to be implemented in OLINDA/EXM version 2. This will include complete adult and pediatric phantom series, based on the standard individuals defined in *International Commission on Radiation Protection Publication 89* (*1*), as well as models representing large and small normal-weight adults, obese adults, and realistic rodent models, for use in dose analyses (*2*).

Members of the RADAR group developed the OLINDA/EXM software, with its technical basis previously established in the literature. Vanderbilt University (Nashville, TN) continues distribution of the code through a 510K mechanism since receiving U.S. Food and Drug Administration approval of the code in 2004. An update of the code, including new decay data and realistic standardized phantoms, is scheduled for 2009. The group is also working on using realistic body models to develop better approaches to the release of nuclear medicine patients, a Web-based calculational tool for calculating doses from radioactive patients to others, updated specific γ exposure constants, and other projects of interest to the nuclear medicine community. The RADAR Web site is continually updated with new and useful information. Any and all suggestions and requests for useful information that could be added to the site are always appreciated.

Other Electronic Resources: Links to many other Web sites with highly useful information, too numerous to describe in detail, can be found on the SNM Web site at http://interactive.snm.org/index.cfm?PageID=944&RPID=10 or the University of Michigan health physics resource page at www.umich.edu/~radinfo/.

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. Subscriptions are free, and digest versions (once-per-day summaries of all posts) are usually available. A large number of Yahoo groups also have relevance to this area of science (but are too numerous to mention) and use bulletin-board approaches to exchange information. The Health Physics Society Web site offers links to these groups at http://hps.org/links.html.

New Dosimetry Literature: Research into various aspects of radiation dosimetry continues to expand, and this interest is reflected in the literature on specific subsets of investigation and analysis.

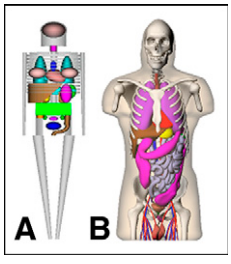

Figure 1. (A) Stylized adult male model and (B) realistic human phantom for internal dosimetry calculations.

New radionuclides. The past year saw significant interest in the use of α particles and Auger emitters in radionuclide therapy. Zalutsky et al. (*3*) kicked off the year with a report on clinical experience with the α-emitting nuclide ^{211}At labeled to a monoclonal antibody in the treatment of recurrent brain cancer in a clinical setting. Neti and Howell (*4*) evaluated the distributions of cellular uptake of α-emitters through particle track autoradiography. Their findings have implications for radiation dosimetry of α-emitters used in therapy. Costantini et al. (*5*) studied the response of breast cancer cells to ^{111}In-NLS-trastuzumab, with the addition of a radiosensitizing agent. Sgouros and Song (*6*) discussed cancer stem cell targeting with the α-emitter ^{213}Bi. Yuan et al. (*7*) discussed the impact of nonuniform activity distributions on cellular dosimetry.

Patient-individualized dose calculations. Standardized dose calculations for reference adults and children have been well documented by the RADAR group and implemented in standard software (*8*); thus, standard dose calculations can be executed by almost anyone with a reasonable understanding of dosimetry fundamentals. In therapeutic uses of radiopharmaceuticals, however, individualized dose calculations should be performed to give the highest possible dose to malignant tissues safely to each patient. Jensen et al. (*9*) presented a method for patient-individualized therapy of thyroid cancer. Stabin and Flux (*10*) published a review article outlining the need for and providing a prescription for more widespread use of patient-individualized therapy. Stabin (*11*) outlined the case for doing patient-specific dosimetry for all therapy patients, attempting to answer objections and cite literature showing that this practice is not only feasible but strongly indicated to facilitate better and more durable patient responses to therapy. Eterovic et al. (*12*) described a method for Graves' disease therapy planning based on dose to thyroid follicular cells. A direct comparison of 2D and 3D dosimetry methods for the use of ^{90}Y-tiuxetan in the therapy of non-Hodgkin's lymphoma was shown by Assié et al. (*13*). Denardo et al. (*14*) eloquently stated the case for using improved drugs, more patient-specific strategies, and combinations of these methods in radioimmunotherapy to improve outcomes for patients.

Release of nuclear medicine patients. Siegel and Marcus (*15*) discussed some of the important issues in the current implementation of Nuclear Regulatory Commission (NRC) recommendations and regulations on this important topic and discussed the need for updating of some of these areas. Paz-Filho et al. (*16*) evaluated a number of cases of the release of iodine therapy patients and their activation of security alarms in public places. Siegel et al. (*17*) showed that current recommendations by the NRC may be considerably overconservative and pointed to an SNM guidance document with more realistic values to use in patient release decisions. Siegel and Silberstein (*18*) revisited this topic in the July edition of *The Journal of Nuclear Medicine*.

Dose and risk. The controversy regarding low doses of ionizing radiation and risk, started by Brenner and Hall in 2007 in a sensationalist article in the *New England Journal of Medicine* (*19*), continued during 2008, with several points of view expressed by many in the interests of reducing doses as much as possible while still providing adequate health care to patients. A number of articles have appeared discussing potential risks of diagnostic levels of radiation, such as those used in CT and PET/CT studies. At the 2008 Radiological Society of North America meeting, Joseph Schoepf, MD, an associate professor of radiology at the Medical University of South Carolina (Charleston), spoke about this issue, stating: "We have been using radiation for the last century to diagnose disease, to steer patient management, and to reduce doubt in medical imaging. And we cannot allow and we cannot afford a public discussion of what we do to be all of a sudden overtaken by radiation fear, considering all the benefits that we provide our patients on a daily basis" (*20*). Pat Zanzonico, PhD, of the Memorial Sloan–Kettering Cancer Center (New York, NY) has developed an analysis of the *numerical* benefits of the use of ionization radiation in several studies (*21*) for comparison with the theoretical risks predicted by the linear/no threshold theory of carcinogenesis. On specific topics, Garsi et al. (*22*) discussed the use of therapeutic levels of ^{131}I in women of childbearing years and as related to pregnancy outcomes. A commentary was provided by Boreham and Dolling (*23*) discussing much of the relevant literature on this important topic. Sisson et al. (*24*) discussed the incidence of Graves' ophthalmopathy associated with radioiodine therapy.

General dosimetry articles of interest. A number of articles on dosimetry of general interest to the nuclear medicine and greater imaging and therapy communities appeared in 2008. Champion et al. (*25*) demonstrated CELLDOSE, a computer code for the study of radiation dose distributions in spherical objects. Meredith et al. (*26*) demonstrated a method for correcting for radioactivity in blood vessels that overlap the spine in images, related to calculation of red marrow dosimetry. A model for canine dosimetry (*27*), designed to complement several in the literature to date for rodent models, was presented. A study of the radioprotective and radiosensitizing effects of rituximab was given by Kapadia et al. (*28*). A study of the dose from ^{18}F-FDG in early pregnancy was performed by Zanotti-Fregonara et al. (*29*). Gould et al. (*30*) discussed dose reduction techniques when performing rest–stress PET/CT procedures. The effective half-life for retention of ^{131}I in thyroid cancer patients was studied by Remy et al. (*31*). Stabin provided 2 analyses of the uncertainties in internal dose calculations for nuclear medicine, first in general (*32*), then specifically in the study of dose calculations in nuclear cardiology (*33*).

A review of kidney dose and response models was published by Wessels et al. (*34*). Vegt et al. (*35*) studied the use of albumin fragments to reduce renal uptake of radiolabeled peptides. Standard dose estimates were provided, using various methods, for a number of agents, including an ^{18}F-labeled receptor ligand (MK-9470) in healthy subjects (*36*), a new cardiac tracer (^{99m}Tc-N-DBODC) (*37*), ^{99m}Tc-HMPAO–labeled monocytes in patients with rheumatoid arthritis (*38*), and an ^{18}F-labeled Arg-Gly-Asp peptide (*39*).

Instrumentation and Analysis Innovations

Much scientific emphasis is placed on the development of instruments and methods that yield quantitatively accurate information on which to base informed clinical judgments. This topic was highlighted by Luisi Mansi in a simulated discussion between St. Thomas and Lord Kelvin in the September 2008 issue of the *European Journal of Nuclear Medicine and Molecular Imaging* and based on a 2007 presentation by Stephen L. Bacharach, PhD (*40*). Details on how to correct for scatter, attenuation, dead time, and other calibration issues are important to instrument designers and scientists computing the results of studies. The accuracy needed depends on what kinds of judgments and what kind of confidence are needed, and these issues affect the ways in which data are collected and analyzed and results interpreted.

Presentations at SNM and European Association of Nuclear Medicine meetings focus mainly on clinical issues, whereas instrumentation and analysis are discussed in greater depth at the annual IEEE Medical Imaging Conference (MIC). The 2008 IEEE MIC was held in Dresden, Germany, with many papers dealing with new developments in imaging technology. Much interest focused on important advances in multimodality imaging, particularly the development of successfully integrated MR and PET imaging devices on a single gantry for simultaneous imaging. Simultaneous functional and anatomic imaging provides support for visual and computational correlations, as well as the opportunity to correct for motion distortions. Attention was given to organ motion distortion correction using standard SPECT and PET systems, but the problem appears to be resolvable by the current generation of real-time combined modality imaging systems.

The merger of MR and nuclear imaging technology awaited the development of high-gain, low-noise, solid-state devices that can operate in high magnetic fields as replacements for photomultipliers (PMs), which cannot perform in such environments. Sessions at the SNM Annual Meeting discussed the essential concepts, with early examples of PET/MR patient images. The IEEE meeting explored the technical issues in greater depth, with much discussion of the replacements for PMs, including avalanche photodiodes (APDs) and silicon photomultipliers (SiPMs) with element sizes as low as 1 mm on a side, which are now available and being tested in working devices. These are being used with lutetium oxyorthosilicate (LSO) and cadmium zinc telluride (CZT) receptors that provide improved 2D resolution. Researchers at Brookhaven National Laboratory (Upton, NY) have built and tested a CZT PET system mounted on the rat cranium for

imaging of unanesthetized brain, and this technique is now being extended to the smaller mouse brain (*41*). At Stanford, investigators have used 1-mm LSO APD arrays to achieve 0.85-mm spatial resolution with 14% energy resolution at 511 keV for use in breast imaging (*42*). These researchers presented data using cross-strip readouts coupled to monolithic CZT detectors (*43*) that avoid the need to match the size of each APD element to individual detector elements. The development and use of solid-state photo detectors, including SiPM arrays, has had a big impact on the high performance of PET imaging devices. High-quality simultaneous MR and PET imaging has been demonstrated in very high magnetic fields (7- and 9T). Phantom tests were presented at the IEEE meeting in Dresden, and clinical illustrations were included in talks at the 2008 SNM Annual Meeting.

Improved PET resolution is being achieved by adding depth of interaction information (DOI) to identify the true coordinates of detected pairs of events. Coding of the DOI is achieved with different methods using individual detector elements and with block detectors using timing and signal shape analysis processing methods to localize the 3D energy deposition events and thereby reduce parallax errors. This is particularly important when the bore size of the imaging system is close to the surface of the body and may be used to increase detection sensitivity. The Chiba group continues to pioneer in these efforts (*44*), as does the University of California–Davis group.

New and improved detector materials continue to evolve. New processes for production of CZT have given this material new life, and practical imaging systems have been built and are in clinical test. Improvements in material quality and cost have resulted in a number of working devices that are being competitively marketed for use in PET and SPECT devices.

LaBr(Cs) has excellent qualities (light output and speed) for PET applications, but its cost is still high. Some demonstrations with modular cameras show potential benefit using current technology (*45*). TlBr is a possible alternative that is much cheaper and has been proposed as a step in the direction of potential development of a whole-body PET imager (*46*).

Image processing methods continue to improve with the increasing availability of high-performance computational resources. One challenging task is to extract kinetic information from fast dynamic imaging sequences. Two new approaches were presented at the Dresden IEEE meeting. The Yale group presented a novel EM algorithm used to extract kinetic parameters from 4D list-mode data with lower variance without the extra time needed to reconstruct individual frames (*47*). An alternate approach was used by the Harvard group to visualize list-mode 4D tomographic data without reconstruction using list-mode PET and time-of-flight PET (*48*). They modeled the human binocular vision system and created a virtual reality environment in which the viewer could change the viewing point and adjust contrast, zoom, and other viewing parameters through a massively parallel computing system. Stereoscopic fusion in the brain was accomplished using a stereoscopic display. In recent years different groups have demonstrated great benefit from advanced graphics capabilities using commodity items (cheap game systems sold for use in the home) and using promising new computational tools.

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The Commission on Health Care Practice

The SNM Commission on Health Care Practice was newly formed last year to oversee and coordinate the work of several existing SNM committees dealing with issues important to nuclear medicine professionals. The Practice Standards, Procedure Standards, Coding and Reimbursement, and Quality Assurance committees are included in this commission. Much of the work of the commission in 2008 involved the efforts of SNM to create criteria for Centers for Medicare & Medicaid Services (CMS) pay-for-performance (PFP) incentives. These incentives currently provide a small supplemental payment for those physicians who meet criteria accepted by CMS, and it is likely that PFP will become increasingly important in the future. The task of identifying relevant PFP criteria is difficult, because hospital-based specialties, such as nuclear medicine, radiology, and pathology, do not easily fit into the typical PFP categories of demonstrated accomplishment. Development of appropriate criteria must go through multispecialty committees of the American Medical Association (AMA) or the National Quality Forum before being accepted by CMS. It is extremely important for SNM to maintain its membership as a specialty society in the AMA if we are to continue to have input into this process. Unless we have a certain percentage of our physician members who are also members of the AMA—a percentage that we do not have at present—we may lose our AMA delegates and thus our voice in the process.

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Integral to the PFP initiative is the development of appropriate practice standards. Nuclear medicine, by its nature, involves multiple specialties. In addition to imaging societies, such as the American College of Radiology (ACR),