Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. This month we have divided the articles into categories of molecular medicine, pediatric nuclear medicine, therapeutic and diagnostic applications, and health physics. However, the lines dividing such categories are increasingly blurred as nuclear medicine capabilities rapidly expand. Many diagnostic capabilities are now enlisted in direct support of and, often, in real-time conjunction with therapies. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role.

Molecular Medicine

^{18}F-FLT PET in DNA Synthesis

Perumal et al. from the Imperial College London (UK) reported in the September 1 issue of *Cancer Research* (2006;66:8558–8564) on a study assessing the potential of 3'-deoxy-3'-^{18}F-fluorothymidine (^{18}F-FLT) PET for early measurement of thymidylate synthase inhibition as a biomarker for de novo synthesis of DNA in anticancer drug development. The study was conducted in a mouse model of radiation-induced fibrosarcoma-1. Tumor-bearing mice and controls were injected with thymidylate synthase inhibitor 5-fluorouracil (5-FU) and imaged with ^{18}F-FLT PET 1–2 hours after injection. Tumors were excised and analyzed. Whole-cell assays indicated a low-level functional role for the type-1 equilibrative nucleoside transporter (ENT), with an increase in type-1 ENT-binding sites per cell from 49,110 in untreated cells to 73,142 in cells treated with 10 μg/mL 5-FU for 2 hours, without a change in transporter affinity. The authors concluded that ^{18}F-FLT PET "can be used to measure thymidylate synthase inhibition as early as 1 to 2 hours after treatment with 5-FU by a mechanism involving redistribution of nucleoside transporters to the plasma membrane."

Cancer Research

PET Monitoring of Transplanted Islets

In an article e-published on September 15 ahead of print in *Molecular Therapy*, Lu et al. from the University of California at Los Angeles School of Medicine expanded on previously published research on islet graft transplantation (see *Proc Natl Acad Sci USA*. 2006;103:11294–11299 and *Mol Ther.* 2004;9:428–435). In this study, they described a recombinant lentivirus that can be used to engineer human islets to express a PET reporter gene for long-term monitoring, with promising implications for the development of therapeutics to prolong graft survival in individuals with type 1 diabetes. The study was conducted in mice in which the transduced islets could be imaged using microPET and a radiolabeled probe approved by the U.S. Food and Drug Administration for clinical use in humans. They found that the initial signal during the first few weeks after transplantation decreased by as much as one-half, which was attributed to islet cell death immediately after transplantion. However, after this initial drop, the magnitude of signals from the implanted islets remained constant when the mice were imaged again over a period of 90 days. Histology confirmed that the implants contained healthy islets with well-distributed PET reporter-expressing cells. The authors concluded that "these studies suggest that PET imaging of lentivirus-transduced islets could provide a safe and feasible method for long-term monitoring of islet graft survival."

Molecular Therapy

^{124}I PET Imaging of EGFR Kinase Activity

Pal et al. from the M.D. Anderson Cancer Center (Houston, TX) and the Memorial Sloan–Kettering Cancer Center (New York, NY) reported in the September/October issue of *Molecular Imaging and Biology* (2006;8: 262–277) on the potential of PET with epidermal growth factor receptor (EGFR) kinase–specific radiolabeled tracers for noninvasive and repetitive imaging of EGFR expression and signaling activity in tumors before and during therapy with EGFR signaling inhibitors. The authors developed and synthesized a ^{124}I-labeled compound (^{124}I-IPQA), which selectively, irreversibly, and covalently binds the adenosine-triphosphate-binding site to activated EGFR kinase but not to inactive EGFR kinase. They conducted additional investigations with modifications of this compound and obtained noninvasive PET images of EGFR activity in A431 subcutaneous tumor xenografts but not in subcutaneous tumor xenografts grown from K562 human chronic myeloid leukemia cells in immunocompromised rats and mice. These results suggest that PET imaging with this approach should allow for identification of tumors with high EGFR kinase signaling activity, including brain tumors expressing EGFRvIII mutants and nonsmall–cell lung cancer expressing gain-of-function EGFR kinase mutants. They noted that additional investigations will be required to optimize the pharmacokinetics of this promising class of molecular imaging agents.

Molecular Imaging and Biology

MicroPET Quantifies Incremental Therapy Results

Also in the September/October issue of *Molecular Imaging and Biology* (2006;8:300–308), Zhang et al. from Millennium Pharmaceuticals, Inc. (Cambridge, MA) reported on a study designed to validate the quantitative metabolic response of tumors to a treatment measured by longitudinal ^{18}F-FDG microPET, a technique that carries significant implications for preclinical evaluation and development of new anticancer agents. The study was conducted in a mouse prostate cancer model with experimental treatment with bortezomib. Severe combined immunodeficiency mice with CWR22 xenografts were treated with bortezomib and imaged with microPET before, during, and after sequential treatments. The authors found that the microPET images showed a reduction of tumor ^{18}F-FDG uptake beginning on day 4, despite a lack of evidence of absolute tumor shrinkage. Using the total tumor tracer uptake as the viable tumor burden, they found an 86% tumor inhibition compared with only a 55% tumor growth inhibition in tumor volume measurement. They concluded that ^{18}F-FDG microPET imaging "can provide an additional dimension of the efficacy of anticancer therapies that may otherwise be underestimated by tumor volume measurement."

Molecular Imaging and Biology

Bone Marrow Cell Injection in Acute MI

In an article published in the September 21 issue of the *New England Journal of Medicine* (2006;355:1199–1209), Lunde et al. from the Rikshospitalet University Hospital (Oslo, Norway) reported on a randomized, controlled trial to investigate the efficacy of intracoronary injection of autologous mononuclear bone marrow cells (BMCs) in patients after acute myocardial infarction (MI). The study included 97 patients with acute ST-elevation MI of the anterior wall treated with percutaneous coronary intervention who were randomly assigned to intracoronary injection of autologous mononuclear BMCs ($n = 47$) or to a control group ($n = 50$). Gated SPECT and echocardiography assessed left ventricular (LV) function at baseline, and MR imaging was performed 2–3 weeks after MI. The imaging procedures were repeated 6 months after the MI. The mean change in LV ejection fraction for all patients as measured by SPECT between baseline and the 6-month follow-up was 7.6% ± 10.4%. Other metrics also indicated that the 2 groups did not differ significantly in changes in LV end-diastolic volume or infarct size and had similar rates of adverse events. The authors concluded that with the methods used, intracoronary injection of autologous mononuclear BMCs appeared to have no effect on global LV function.

New England Journal of Medicine

Pediatric Applications

SPECT vs MR in Active Spondylolysis

In an article e-published on September 15 ahead of print in the *British Journal of Sports Medicine*, Masci et al. from the University of Melbourne (Australia) reported on evaluation of the one-legged hyperextension test in the diagnosis of active spondylolysis and compared the accuracy of MR imaging with the current gold standard of bone SPECT and CT in the diagnosis of this condition. The study included 71 young athletes with low back pain who were assessed clinically with the one-legged hyperextension test and imaged with bone SPECT and MR. CT was performed when bone scintigraphy was positive. SPECT indicated that 50 pars interarticulares in 39 (54.9%) individuals showed evidence of active spondylolysis. Among these patients, subsequent CT indicated that 19 pars interarticulares in 14 individuals showed fracture. The one-legged hyperextension test proved neither sensitive nor specific for the detection of active spondylolysis. MR imaging identified bone stress in only 40 of the 50 pars interarticulares detected on SPECT. However, MR identified 18 out of 19 pars interarticularis fractures detected by CT. The authors concluded that these results suggest a previously unproven high rate of active spondylolysis in athletes with low back pain. They noted that the one-legged hyperextension test is not useful in the diagnostic process and that MR imaging is inferior to the sequential combination of bone SPECT and CT. Bone scintigraphy, they wrote, "should remain the first-line investigation of active athletes with low back pain followed by limited CT if bone scintigraphy is positive."

British Journal of Sports Medicine

PET in Pediatric Bone Sarcoma

Kneisl et al. from the Carolinas Medical Center (Charlotte, NC) reported in the September issue of *Clinical Orthopaedics and Related Research* (2006;450:101–104) on a study designed to evaluate the use of ^{18}F-FDG PET to detect occult nonpulmonary metastases in patients younger than 30 who were newly diagnosed with either Ewing's or osteosarcoma. The retrospective study included 55 patients. All had undergone PET imaging. PET detected metastases in 12 patients (22%), of whom 8 (67%) were seen to have disease outside the lung. Only 4 (3 with Ewing's sarcoma, 1 with osteosarcoma) of the 55 patients (7%) were upstaged to stage IV specifically as a result of PET findings. The most important alteration in treatment decisions caused by the use of PET was the substitution of radiation for surgery for local control in patients with Ewing's sarcoma.

Clinical Orthopaedics and Related Research

rhTSH in Pediatric Thyroid Cancer

In the September issue of the *Internal Medicine Journal* (2006;36:564–560), Lau et al. from the Peter MacCallum Cancer Centre (Melbourne, Australia) reported on experience in the management of differentiated thyroid carcinoma in children, with a focus on the use of radioiodine after administration of recombinant human thyroid stimulating hormone (rhTSH). The study

included 8 patients (age range, 7–17 years) who had undergone total thyroidectomy for thyroid carcinoma (7 for papillary carcinoma and 1 for follicular carcinoma). Four patients had previously undergone radiation treatment. Five had known lymph node metastases, and 1 had pulmonary metastases at the time of the study. All 8 patients underwent diagnostic iodine scans, 7 with rhTSH stimulation. Seven patients proceeded to ^{131}I treatment. Seven of 8 patients had significant uptake in the neck on diagnostic scan, and 2 had pulmonary uptake. Six of the 7 evaluable patients achieved complete thyroid ablation. Both patients with pulmonary abnormalities later achieved scan resolution. All patients were administered thyroxine replacement to suppress TSH, and all remained alive at the time the study was prepared for publication. The authors concluded that optimal management of pediatric thyroid carcinoma requires a multidisciplinary approach and that "radioiodine therapy under rhTSH is an effective and safe adjuvant treatment in this special subgroup."

Internal Medicine Journal

Diagnosis

Endothelin-1 Effects on PET Perfusion Imaging

Loghin et al. from the University of Texas Medical School (Houston) reported on September 1 ahead of print in the *American Journal of Physiology: Heart and Circulatory Physiology* on a study designed to test the hypothesis that the intracoronary vasoconstrictor endothelin-1 may cause myocardial perfusion abnormalities on resting PET imaging that may persist or improve only partially after stress challenge in the absence of myocardial scar and flow-limiting stenosis. The study included 14 dogs that underwent serial ^{82}Rb PET perfusion imaging before and after subselective intracoronary infusion of endothelin-1, followed by intravenous and then intracoronary adenosine. Small doses of endothelin-1 infused into the mid left circumflex coronary artery caused significant resting perfusion abnormalities that normalized after intracoronary adenosine but not consistently after the intravenous adenosine administration used for diagnostic imaging. After the adenosine effects ended, resting perfusion defects returned, lasting up to 5 hours in some animals. The total cumulative doses of endothelin-1 caused perfusion defects that did not normalize after intravenous adenosine. The authors concluded that in this setting intracoronary endothelin-1 causes visually apparent, quantitatively significant, long-lasting myocardial perfusion defects at resting conditions that may persist or only partially improve after intravenous adenosine used for diagnostic imaging.

American Journal of Physiology: Heart and Circulatory Physiology

SPECT Ties Dyspnea with CAD

In an article in the September issue of the *American Heart Journal* (2006; 152:551–557), Balaravi et al. from the Mayo Clinic (Rochester, MD) reported on a study examining the prevalence, severity, and prognostic value of perfusion defects detected by SPECT imaging in patients with dyspnea. The study included 1,864 patients (ages, 65.8 ± 10.2 years; 52% men, 48% women; 23% diabetic; and 89% overweight or obese) without known coronary artery disease (CAD) who were referred for evaluation of mild, moderate, or severe dyspnea. All underwent SPECT imaging, where perfusion defects were categorized as low, intermediate, or high risk. Forty-five percent of patients had abnormal perfusion SPECT findings, and 11% had high-risk findings. Male sex, diabetes, and clinical severity of dyspnea were the strongest predictors of both abnormal and high-risk imaging findings. At 10 years, survival rates in each of the SPECT findings categories were: low risk, 75%; intermediate risk, 68%; and high risk, 53%. The high prevalence of abnormal and high-risk perfusion defects—and directly correlated 10-year survival rates—noted in this population of older overweight patients led the authors to suggest that SPECT and other assessments for CAD might be considered as routine adjuncts in the diagnosis and management of dyspnea.

American Heart Journal

Diabetes and Myocardial Glucose Uptake in CAD

Sondergaard et al. from the Arrhus University Hospital (Denmark) reported on September 19 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on a study of the relationship between type 2 diabetes mellitus and coronary artery disease (CAD). The study included 27 patients with coronary artery disease (left ventricular ejection fraction [LVEF] >50%; 12 with type 2 diabetes and 15 without). All patients underwent PET imaging to determine regional myocardial and skeletal glucose uptakes and skeletal muscle perfusion. Myocardial perfusion was measured at rest and during hyperemia in nonstenotic and stenotic regions with and without acute hyperinsulinemia. They found that myocardial glucose uptake was similar in both groups of patients, in stenotic and nonstenotic regions. Skeletal and whole-body glucose uptakes were reduced in the diabetic group. Insulin did not alter myocardial blood flow at rest or during hyperemia. Insulin increased skeletal blood flow in patients without diabetes but not in those with the disease. The authors concluded that, contrary to previous suggestions, myocardial insulin resistance to glucose uptake is not an inherent feature in patients with type 2 diabetes who have preserved LVEF. Moreover, "acute physiological insulin exposure exerts no coronary vasodilation in CAD patients" regardless of whether they have diabetes.

Journal of Clinical Endocrinology and Metabolism

PET vs WBC Imaging in Prosthetic Hip Infection

Reporting in the September supplement to the *Journal of Arthoplasty* (2006;21[suppl 6]:91–97), Pill et al. from the University of Pennsylvania

(Philadelphia) compared the accuracy of ^{18}F-FDG PET with that of ^{99m}Tc sulfur colloid ^{111}In-labeled white blood cell (WBC) scintigraphy in the diagnosis of periprosthetic infection. The study included 89 patients with 92 painful hip prostheses who were given the option of undergoing either combined PET and WBC imaging or PET only. PET imaging (performed in all patients) correctly diagnosed 20 of the 21 infected cases (sensitivity, 95.2%) and ruled out infection in 66 of 71 noninfected hips (specificity, 93%), with a positive predictive value of 80% and a negative predictive value of 98.5%. WBC imaging correctly identified 5 of the 10 infected hips (sensitivity, 50%) in which it was applied and 39 of 41 aseptic hips (specificity, 95.1%), with positive and negative predictive values of 41.7% and 88.6%, respectively. The authors concluded that these results suggest that ^{18}F-FDG PET is "a promising diagnostic tool for distinguishing septic from aseptic painful hip prostheses."

Journal of Arthoplasty

Functional Asymmetry in Donor Kidneys

Oh et al. from the Ajou University School of Medicine (Yeongtong-Gu, Korea) reported in the September issue of *Transplant Proceedings* (2006;38: 1971–1973) on a study using ^{99m}Tc-diethylenetriamine pentaacetic acid scintigraphy to assess renal functional asymmetry as part of routine prenephrectomy evaluation in potential kidney donors. The study included 100 potential donors, who underwent scintigraphy and from whom 24-hour urine studies were obtained to measure serum creatinine and creatinine clearance. On average, the left kidneys showed greater function (51.67%–53.35%). The average fraction of creatine clearance for left kidneys was higher than that for the right kidneys. Although no significant differences were noted in either donor or recipient clinical course based on left or right origin of the kidney, the authors noted that the findings in this study suggest that it may be prudent to "pay attention to possible functional kidney asymmetry" when choosing between left and right nephrectomy.

Transplant Proceedings

Therapy

^{18}F-FPA PET and Boron Neutron Capture Therapy

Aihara et al. from the Kawasaki Medical School (Kurashiki, Japan) reported in the September issue of *Head and Neck* (2006;28:850–855) on boron neutron capture therapy (BNCT) for head and neck tumors and on the application of their technique in a woman with recurrent submandibular gland cancer. ^{18}F-boronophenylalanine PET (^{18}F-BPA PET) was first used to verify the ability of the tumor to concentrate boronophenylalanine. The patient underwent CT imaging for treatment planning, and the tumor was irradiated with epithermal neutrons at 5 MW for 90 minutes, with a tumor dose = 20.0–25.2 Gy and normal tissue dose = 3.2–5.8 Gy. At 1.5-year follow-up, the patient continues in complete tumor regression with no acute or chronic complications. The authors suggest that additional studies should make use of this technique and that the excellent results shown here for BNCT "will have a great impact on patients in the near future."

Head and Neck

^{131}I-Labeled mAb RIT in Colon Cancer

In an article e-published ahead of print on September 15 in the *International Journal of Radiation Oncology, Biology, and Physics*, Li et al. from the State Key Laboratory of Cancer Biology and the Fourth Military Medical University (Xi'an, China) reported on the therapeutic efficacy, suitable dose, and administration times of ^{131}I-CAb(1) F(ab')(2), a new monoclonal antibody therapeutic compound specifically directed against a cell surface-associated glycoprotein of colon cancer. The study was conducted in mice bearing human colon cancer xenografts. Different doses of ^{131}I-CAb(1) F(ab')(2) were administered on days 6 and 18 after implantation of HR8348 cells with CAb(1) high reactivity. Treatment with 125, 375, or 1,125 μCi of the radiolabeled compound did not significantly decrease mean survival time for mice when compared with control groups. The mean survival times of mice receiving the 2 higher dosages (375 or 1,125 μCi) were significantly longer than those of other experimental groups. Tumor growth inhibition rates in the ^{131}I-CAb(1) F(ab')(2)-treated group at day 20 were 42.65% for the 125 μCi group, 56.56% for the 375 μCi group, and 84.4% for the 1,125 μCi group. The authors concluded that ^{131}I-CAb(1) F(ab')(2F(ab')(2) is safe and effective for colon cancer and may be a novel and potentially adjuvant therapeutic approach in the disease.

International Journal of Radiation Oncology, Biology, and Physics

Gender Comparisons in RIT Dosimetry

Lehmann et al. from the University of California Davis School of Medicine (Sacramento) reported on September 8 ahead of print in the *International Journal of Radiation Oncology, Biology, and Physics* on a study assessing the absorbed radiation dose in normal tissues for prostate cancer patients compared with that in breast cancer patients for 2 radiopharmaceuticals using the monoclonal antibody (mAb) m170. ^{111}In-DOTA-GGGF-m170 and ^{111}In-1,4,7,10-DOTA-2IT-m170 (the same MAb and chelate with and without a cleavable linkage) were studied in 13 patients with breast cancer and 26 patients with prostate cancer. Dosimetry for ^{90}Y was calculated using ^{111}In mAb pharmacokinetics from the initial imaging study for each patient and reference man- and patient-specific masses. The calculated results were not significantly different for breast and prostate cancer patients for both radiopharmaceuticals, with the exception of 1 combination (liver and DOTA-2IT). Most of the patient-specific dose differences

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could be attributed to weight differences. The authors concluded that the results of this study, indicating that similar normal tissue doses were calculated for 2 groups of patients with different cancers and genders, might be combined with continued careful analysis of the imaging data to "allow the use of higher starting doses in early-phase radioimmunotherapy studies."

International Journal of Radiation Oncology, Biology, and Physics

Health Physics

PET/CT Exposure of Technologists

Seierstad et al. from the Buskerud University College (Drammen, Norway) reported on September 20 ahead of print in *Radiation Protection and Dosimetry* on a study designed to map doses to technologist staff members after the installation of Norway's first dedicated PET/CT installation in 2005. The results of the study, which are consonant with those from other studies, calculated an average technologist dose of 20–25 nSv per injected MBq of ^{18}F. For an average injected activity of 350 MBq per patient, the International Committee on Radiologic Protection dose limit would be reached after imaging approximately 3,000 patients in a single year. For the authors' annual number of less than 500 patients and routine rotation of staff, an annual individual dose for the technologists was calculated at less than 2–3 mSv.

Radiation Protection and Dosimetry

IAEA Issues QA Guidance

In an article e-published ahead of print in the October/November issue of *Applied Radiation and Isotopes* (2006;64:1142–1146), Zimmerman et al. from the International Atomic Energy Agency (IAEA) reported briefly on a new guidance document issued by the agency for the implementation of quality assurance programs for nuclear medicine radioactivity measurement. The proposed programs are designed to enable laboratories, particularly those in developing countries, to provide consistent, safe, and effective radioactivity measurement services to the medical community. Details about the guidance should be available at www.iaea.org

Applied Radiation and Isotopes

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delivery vehicles to target new diagnostic approaches such as smart contrast agents, target-specific optical agents, and cell-based (stem cell) imaging and also to deliver gene therapy and other innovative interventions to patients. SNM recognizes the importance of ensuring that its members have the skills to be part of this diagnostic and therapeutic evolution.

Drug Development: The appropriate use of molecular imaging in drug discovery and development could significantly speed up the development process and save patients and the health care system millions of dollars. Molecular imaging techniques are already being used in receptor occupancy studies and with transgenic animal models to validate drug development. In all phases of clinical trials, molecular imaging probes will play an increasingly important role in developing new, smarter, and safer drugs for patients.

In Clinical Practice: Work will continue to examine and validate future clinical applications for FDG PET/CT for oncology, myocardial perfusion, neurology and neurosurgery, infection imaging, and other applications. The next generation of clinical radiotracer probes is already in early phase clinical development. The SNM Clinical Trials Group will ensure that these probes are appropriately validated and accepted by funders to enhance all aspects of patient care. Bioluminescence imaging, which enables visualization of genetic expression and physiological processes at the molecular level in living tissues, may identify, for example, metastatic potential and predict treatment effects.

Education and Training: We must see an evolution in the education of physicians to fully and effectively utilize changes in practice as molecular medicine and molecular imaging become part of routine clinical practice and as new probes and technologies are developed and translated into clinical practice. SNM is committed to ensuring that our members are uniquely placed to benefit from these health care advances.

As new research is performed and new modalities unfold, molecular imaging will continue to expand and grow, providing SNM the opportunity to contribute to improvements in patient care in a meaningful, positive, and cost-effective way.

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