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. 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. We have added a special section on molecular imaging, including both radionuclide-based and other molecular imaging efforts, in recognition of the extraordinary activity and promise of diagnostic and therapeutic progress in this area. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.

DIAGNOSIS

Visual Estimation of CAC

In the November 30 issue of the *Journal of the American College of Cardiology* (2010;56:1914–1921), Einstein et al. from the Columbia University Medical Center (New York, NY) evaluated the accuracy and reproducibility of visual estimation of coronary artery calcium (CAC) from CT attenuation correction scans performed for PET/CT and SPECT/CT myocardial perfusion imaging (MPI). The study included 492 patients from 3 centers who received both MPI and CT attenuation correction scans and a standard CAC scan. Readers without access to Agatston scores visually estimated CAC from the CT attenuation scans on a 6-level scale: estimated Agatston scores of 0, 1–9, 10–99, 100–300, 400–999, or ≥1,000. Agreement between these visually estimated CAC levels and separately obtained Agatston scale results (converted to the same 6-level classification) was assessed. The researchers found a high degree of association between the visually estimated CAC levels and separately obtained Agatston scale results, with 64% of the previous in the same categories as the latter, and 93% within 1 category on either side. Moreover, reader agreement was good, with identical scores in 65% of cases and within 1 category on either side in 93%. The authors concluded that despite the fact that CT attenuation correction scans are relatively low dose and are ungated, CAC can be visually assessed from these scans "with high agreement with Agatston scale" results. They added that "CT attenuation scans should be routinely assessed for visual estimation of CAC."

Journal of the American College of Cardiology

Bone Marrow Cells and Myocardial Viability

Roncalli et al. from the CHU/INSERM and Université Paul Sabatier (Toulouse, France) reported on December 2 ahead of print in the *European Heart Journal* on a multicenter study designed to evaluate the effect of intracoronary autologous bone marrow cell therapy on myocardial viability in patients with decreased left ventricular ejection fraction (LVEF) after acute myocardial infarction and to identify predictive factors for viability improvement. The study included 101 patients with acute myocardial infarction and successful reperfusion, LVEF ≤ 45%, and decreased myocardial viability (as assessed by ^{201}Tl SPECT). Baseline mean LVEF at radionuclide angiography was 36.3% ± 6.9%. Patients were randomized to a control group (n = 49) or a therapy group (n = 52). Myocardial viability was reassessed at 3 mo after infarction. Bone marrow cell infusion was performed 9.3 ± 1.7 d after infarction in the therapy group. Myocardial viability improved in 16 of 47 (34%) patients in the therapy group and 7 of 43 (16%) in the control group. Multivariate analyses including prognostic factors showed much greater improvement in myocardial viability in the therapy group than in the control group. A significant adverse role for active smoking and a positive trend for microvascular obstruction were noted. The authors concluded that "intracoronary autologous bone marrow cell administration to patients with decreased LVEF after acute myocardial infarction was associated with improvement of myocardial viability in multivariate—but not in univariate—analysis" and that a large multicenter trial is needed to further document this therapy and better characterize those patients who will benefit.

European Heart Journal

PET and Meth in the Human Body

In an article appearing on December 7 in the online journal *PLoS One* (2010;5:e15269), Volkow, from the National Institute on Drug Abuse (Bethesda, MD), and colleagues from the Brookhaven National Laboratory (Upton, NY), reported on a study using PET to measure methamphetamine's organ distribution and pharmacokinetics in the human body. The study included 19 healthy participants (9 Caucasians, 10 African Americans) who underwent ^{11}C-D-methamphetamine PET imaging to measure whole-body distribution and bioavailability as assessed by peak uptake (% dose/cc), rate of clearance (time to reach 50% peak clearance), and accumulation (area under the curve). Methamphetamine was found to distribute through most organs, with the highest uptake (whole organ) in the lungs (22% dose; weight ~1246 g) and liver (23% dose; weight ~1677 g). Uptake was intermediate in the brain (10% dose; weight ~1600 g). High uptake on a per cubic centimeter basis was

also found in the kidneys (7% dose; weight 305 g). Clearance was fastest in heart and lungs (6–7 min); slowest in brain, liver, and stomach (>75 min); and intermediate in kidneys, spleen, and pancreas (22–50 min). Of note was that fact that lung accumulation of the radiolabeled methamphetamine was 30% higher for African Americans than Caucasians but did not differ in other organs. The authors concluded that "the high accumulation of methamphetamine, a potent stimulant drug, in most body organs, is likely to contribute to the medical complications associated with methamphetamine abuse." They speculated that methamphetamine's high pulmonary uptake could render this organ vulnerable to infections (tuberculosis) and pathology (pulmonary hypertension). They noted that the preliminary findings of higher lung accumulations of methamphetamine in African Americans merit further investigation and question whether this differential could contribute to the less frequent use of methamphetamine among African Americans.

PLoS One

PET and Long-Term Effects of MDMA

In an article e-published on December 15 ahead of print in *Neuropsychopharmacology*, Tai et al. from the Imperial College London (UK) used ^{18}F-DOPA PET to investigate the long-term effects of the drug "ecstasy" (3,4-methylenedioxymethamphetamine [MDMA]) on nigrostriatal dopaminergic function in a group of male ex-users. The study included 14 ex-ecstasy users who had been abstinent for a mean of 3.22 y, 14 polydrug-using controls (matched to the ex-users for other recreational drug use), and 12 drug-naive controls. Each study participant underwent ^{18}F-DOPA PET imaging, cognitive assessments, and hair and urinary analyses to corroborate drug-use history. Ex-ecstasy users showed a putamen ^{18}F-DOPA uptake that was 9% higher than that of the drug-naïve controls, with the uptake of the polydrug-using group falling between these 2 groups. The authors indicated that this suggests that the hyperdopaminergic state in ex-ecstasy users may be the result of the combined effects of ecstasy and polydrug use. No correlation was found between the amount of ecstasy used and striatal ^{18}F-DOPA uptake. The authors concluded that increased putaminal uptake after an abstinence of >3 y suggests that effects on nigrostriatal dopaminergic function are long lasting and that use in conjunction with other recreational drugs is a factor to be considered in further longitudinal studies.

Neuropsychopharmacology

Next-Day Effects of OTC Sleep Meds

Zhang et al. from the Tohoku University Graduate School of Medicine (Miyagi, Japan) reported in the December issue of the *Journal of Clinical Psychopharmacology* (2010;30: 694–701) on a PET study of the next-day residual sedative effects of an over-the-counter (OTC) antihistamine sleep aid and a second-generation antihistamine. The study included 8 healthy men who underwent PET assessment in the morning after randomized oral administration of diphenhydramine (50 mg), bepotastine (10 mg), or placebo at 11:00 PM the previous night. Binding potential ratios and brain H_1 receptor occupancy were calculated in different brain areas, plasma drug concentrations were measured, and subjective sleepiness was assessed. The researchers found significantly lower binding potential ratio values for diphenhydramine than for bepotastine or placebo in all regions of interest. Cortical mean brain H_1 receptor occupancy after diphenhydramine was 44.7%, compared with 16.6% for bepotastine treatment. Subjective sleepiness assessments did not vary among the treated subjects and controls. The authors summarized their findings: "Next-day residual sedative effect after nighttime administration of the OTC sleep aid diphenhydramine was verified for the first time by direct PET measurement of brain H_1 receptor occupancy." They added that "taking into account the possible hangover effect of OTC antihistamine sleep aids, care needs to be taken during their administration."

Journal of Clinical Psychopharmacology

THERAPY

RIT vs Chemotherapy in Colorectal Cancer

In an article e-published on December 15 ahead of print in the *British Journal of Surgery*, de Jong et al. from Radboud University Nijmegen Medical Centre (The Netherlands) reported on a study designed to investigate the survival benefits of radioimmunotherapy (RIT) compared with those of chemotherapy for colorectal cancer in an experimental model. Rats were injected with CC531 tumor cells, and the therapeutic efficacy of the ^{177}Lu-labeled monoclonal antibody MG1 (single intravenous dose) was compared with that of 5-fluorouracil–based chemotherapy (6 weekly cycles administered intraperitoneally) and with results in a control group with no treatment. The researchers found that although both chemotherapy and RIT affected body weight, the weight of animals in the RIT group remained significantly higher than that in the chemotherapy group. Overall survival in the RIT and chemotherapy groups was significantly longer than that in the control group (50% 46%, and 25%, respectively) after 170 d, but survival after RIT did not differ significantly from that after chemotherapy. The authors concluded that "RIT is as effective as chemotherapy in experimental colorectal cancer."

British Journal of Surgery

Zevalin and MALT Lymphoma

Hoffmann et al. from the Medical University Vienna (Austria) reported on December 6 ahead of print in *Leukemia and Lymphoma* on a study of ^{90}Y-ibritumomab tiuxetan radioimmunotherapy (RIT) in heavily pretreated patients with mucosa-associated lymphoid tissue (MALT) lymphoma. The study included

6 patients who were progressing or relapsing after conventional therapy for MALT lymphoma (2 gastric, 1 orbital, 2 cutaneous, 1 with widely disseminated lymphoma involving the stomach, lungs, lymph nodes, and salivary glands). All were experiencing at least a third relapse after various treatments, including Helicobacter pylori–eradication, radiation, chemotherapy, and rituximab. After 2 doses of rituximab at an interval of 1 week, ^{90}Y-ibritumomab tiuxetan was immediately administered. Treatment was well tolerated, except for 1 patient who was hospitalized with pneumonia. Four patients developed complete remission (ongoing at the time of publication for 4, 16, 23, and 24 mo), 1 patient had a partial response lasting for 5 mo, and 1 patient had stable disease for 13 mo. At 29 mo after treatment, all patients were alive. The authors concluded that "application of ^{90}Y-ibritumomab tiuxetan is active and safe in heavily pretreated patients with MALT lymphoma."

Leukemia and Lymphoma

MOLECULAR IMAGING

Combination Carbon Ion Radiotherapy

Ohkubo et al. from the National Institute of Radiological Sciences (Chiba, Japan) reported in the December 1 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2010;78:1524–1531) on an experimental study combining carbon ion radiotherapy and local injection of α-galactosylceramide-pulsed dendritic cells in a murine model of lung metastases. Squamous cell carcinoma cells in tumors in the legs of C3H/HeSlc mice were locally irradiated with a single 6-Gy dose of carbon ions. The following day, α-galactosylceramide-pulsed dendritic cells were injected into the leg tumors. A control group of tumor-inoculated mice received no treatment. Mice that received the combination therapy presented with 2.6 ± 1.9 metastatic nodules in the lungs, whereas mice with no treatment presented with 168 ± 53.8 such nodules at 2 wk after irradiation. Immunohistochemistry indicated that intracellular adhesion molecule 1, which activates dendritic cells, increased after irradiation in local tumors in the therapy group. The expression of S100A8 in lung tissue, a marker of premetastasis, was decreased in the therapy group but not in the controls. The authors concluded that "the combination of carbon ion radiotherapy with the injection of α-galactosylceramide-pulsed dendritic cells into the primary tumor effectively inhibited distant lung metastases."

International Journal of Radiation Oncology, Biology, Physics

NIRF Imaging of Lymphatic Transport

Rasmussen et al. from the University of Texas Health Science Center at Houston (TX) reported in the December 1 issue of *Translational Oncology* (2010;3:362–372) on a study using dynamic near-infrared (NIR) fluorescence to image lymphatic architecture and dynamic transport in healthy individuals and patients diagnosed with unilateral lymphedema. Indocyanine green was injected intradermally bilaterally in the arms or legs of controls and patients, and active lymphatic propulsion was imaged. Well-defined lymphatic structures with propulsive dye transport were seen in the limbs of healthy subjects, whereas the limbs of patients showed extravascular dye accumulation, networks of fluorescent lymphatic capillaries, and/or tortuous lymphatic vessels in symptomatic and even some asymptomatic limbs. Additional analysis showed that disease status significantly affected lymph propagation velocity and contractile frequency. The authors concluded that these clinical research studies "demonstrate the potential of NIR fluorescence imaging as a diagnostic measure of functional lymphatics and as a new tool in translational research studies to decipher the role of the lymphatic system in cancer and other diseases."

Translational Oncology

^{99m}Tc-Labeled Nanoparticles

In an article e-published on December 16 ahead of print in *Molecular Imaging and Biology*, Areses et al. from the University Clinic of Navarra (Pamplona, Spain) reported on molecular imaging techniques to study the biodistribution of orally administered ^{99m}Tc-labeled naïve and ligand-tagged nanoparticles. Conventional polyanhydride nanoparticles and cyclodextrin-tagged nanoparticles were radiolabeled with ^{99m}Tc and assayed for purity and size. SPECT/CT was used for molecular imaging to assess biodistribution in small animal studies. Imaging showed activity only in the gastrointestinal tract, with 13% of the administered dose of the cyclodextrin-tagged nanoparticles and 3% of the polyanhydride nanoparticles remaining in the stomach at 8 h. No evidence of distribution outside the gastrointestinal tract was found. The authors attributed the fact that the cyclodextrin-tagged nanoparticles moved significantly more slowly inside the gut to their physicochemical structure, which allows stronger interactions with the gut mucosa.

Molecular Imaging and Biology

Imaging T-Cell Proliferation

Patel et al. from Stanford University (CA) and National Yang-Ming University (Taipei, Taiwan) reported in the December 15 issue of *Cancer Research* (2010;70:10141–10149) on longitudinal, noninvasive imaging of T-cell effector function and proliferation in living subjects. The authors described in detail a process for linking a reporter gene to the Granzyme B promoter (pGB), which has transcriptional activity that is known to increase during T-cell activation. Two signal amplification strategies were employed. One of these, the cytomegalovirus enhancer (CMVe) strategy to maximize firefly luciferase reporter gene expression, achieved a level of bioluminescence activity sufficient for noninvasive imaging in mice. With T cells transduced with a reporter vec-

tor containing the hybrid pGB-CMVe promoter, the group was able to optically image T-cell effector function over time in response to tumor antigens in living mice. They concluded that this methodology "has the potential to accelerate the study of adoptive immunotherapy in preclinical cancer models."

Cancer Research

REVIEWS

Review articles provide an important way to stay up to date on the latest topics and approaches and provide valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in December. These include "Approaching MALDI molecular imaging for clinical proteomic research: current state and fields of application," by Rauser et al. from the German Research Center for Environmental Health (Neuherberg, Germany) in the December issue of *Expert Review of Proteomics* (2010;7:927–941); "In vivo biodistribution of stem cells using molecular nuclear medicine imaging," by Welling et al. from the Leiden University Medical Center (The Netherlands) on December 6 ahead of print in the *Journal of Cell Physiology*; "Nucleic acid aptamers for clinical diagnosis: cell detection and molecular imaging," by Soontomworajit and Wang from the University of Connecticut (Storrs) ahead of print in the December 15 issue of *Analytical and Bioanalytical Chemistry*; and "Current concepts and future directions in radioimmunotherapy," by Lin and Iagaru in the December 1 issue of *Current Drug Discovery Technologies* (2010;7:253–262)

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