



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. Note that although we have divided the articles into diagnostic and therapeutic categories, these lines 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. This month, the literature yielded an unusually high number of articles on nuclear medicine techniques in neurologic and psychiatric assessment applications.

Diagnosis

PET in Assessment of Abuse Potential

In the March 15 issue of *Biological Psychiatry* (2005;57:640–646), researchers from the Brookhaven National Laboratory (Upton, NY) and the State University of New York at Stony Brook reported on a novel use of PET to predict abuse potential for a new antidepressant based on dopamine transporter (DAT) occupancy. Volkow et al. in previous studies have described the use of PET in assessing possible reinforcing effects of DAT-blocking drugs. These studies have shown that such drugs must block more than 50% of DAT within a relatively short period of time (<15 minutes after administration) to produce reinforcing effects. In the current study, they assessed the potency and pharmacokinetics of DAT blockade induced by the new antidepressant

drug *radafaxine* ([2S,3S]-2-[3-chlorophenyl]-3,5,5-trimethyl-2-morpholinol hydrochloride). *Radafaxine* is a potent metabolite of *bupropion* that is being evaluated both as a treatment for depression and for possible use in treatment of obesity. The study included 8 healthy men who underwent ^{11}C -cocaine PET imaging at 1, 4, 8, and 24 hours after *radafaxine* administration. The authors found that DAT blockade by *radafaxine* was slow, reaching 11% at 1 hour and a peak blockade of 22% at 4 hours. The maximum blockade in any single subject was 33%. No adverse effects were noted. They concluded that the relatively low potency of *radafaxine* in blocking DAT, its slow pharmacokinetics, and its steady-state DAT blockade suggest that *radafaxine* “is likely to have minimal or no reinforcing potential and is therefore unlikely to be abused.”

Biological Psychiatry

PET Sees Parkinson's Progression as Nonlinear

Hilker et al. from the University of Cologne (Germany) reported in the March issue of the *Archives of Neurology* (2005;62:378–382) on a study using ^{18}F -fluorodopa PET to determine the progression of striatal dopaminergic impairment in patients with Parkinson's disease (PD). The study included 31 individuals with a wide range of PD symptom duration and severity and also included a group of healthy controls. Baseline ^{18}F -fluorodopa PET imaging was followed up for periods averaging 64.5 months. In patients with PD, the rate of decline in the putamen ^{18}F -fluorodopa uptake constant correlated inversely with disease duration before entering the study. Annual disease progression rates ranged from 4.4% in the caudate nucleus to 6.3%

in the putamen. The authors concluded that these and other data “suggest that the neurodegenerative process in PD follows a negative exponential course and slows down with increasing symptom duration, contradicting the long-latency hypothesis of PD.”

Archives of Neurology

PET and rCBF in Cocaine Use Disorder

In an article e-published ahead of print in the March 9 issue of the *Journal of Cerebral Blood Flow and Metabolism*, Johnson et al. from the University of Virginia (Charlottesville) used H_2^{15}O PET in the investigation of cocaine's dose-dependent, time-related effects on regional cerebral blood flow (rCBF) in 31 individuals with cocaine use disorder. Participants were divided into 2 groups administered (a) a low dose of cocaine or a placebo and (b) a high dose of cocaine or a placebo, with testing of different dose conditions in the same individual separated by a period of at least 48 hours. At each test, individuals underwent H_2^{15}O PET to assess rCBF. Global and regional hypoperfusion were associated with both low- and high-dose cocaine conditions but not with placebo administration. The hypoperfusion effects of cocaine peaked at 8 minutes. The authors noted that although cocaine-induced hypoperfusion occurred throughout the brain, the left hemispheric dopamine-rich sublobar region was the most severely affected. They concluded that increasingly larger doses of cocaine may be associated with greater risk for ischemic stroke, particularly in this area of the brain.

Journal of Cerebral Blood Flow and Metabolism

PET and Effects of Smoking

In an article published in the March issue of the *American Journal of Psychiatry* (2005;162:567–577), Zubieta et al. from the University of Michigan (Ann Arbor) reported on the effects of cigarette smoking on regional cerebral blood flow (rCBF). The study included 19 tobacco smokers who were studied with ^{15}O -water PET after overnight abstinence. A baseline scan was obtained, and each individual was scanned before and after smoking 3 consecutive cigarettes. Participants were also surveyed for subjective feelings of nicotine craving. The researchers found that smoking the first cigarette of the day resulted in increases in rCBF in the visual cortex and cerebellum and reductions in the anterior cingulate, right hippocampus, and ventral striatum. Cigarette craving scores correlated with some but not all of these rCBF changes. Subsequent cigarettes had similar but reduced effects. The authors noted that these PET data indicate that smoking affects rCBF in areas implicated in the rewarding effects of drugs of abuse and that areas associated with cigarette craving match those previously associated with drug craving and relapse to drug-seeking behavior.

American Journal of Psychiatry

Dopamine and Working Memory

Aalto et al. from the University of Turku (Finland) reported in the March issue of the *Journal of Neuroscience* (2005;25:2471–2477) on the use of PET and a high-affinity dopamine D2 receptor in the study of working memory function in healthy humans. The study included 12 volunteers who underwent ^{11}C -FLB-457 PET imaging while performing verbal working memory and sustained attention tasks. The authors noted reduced D2 receptor availability in the left ventral anterior cingulate in both tasks and reduced D2 receptor availability in the ventrolateral frontal cortex bilaterally and in the amygdala

and hippocampus in the verbal working memory task, suggesting increased dopamine releases in these areas. Their results also indicated that, in the working memory task, increased dopamine release in the right ventrolateral frontal cortex was associated with faster performance and that increased dopamine release in the left ventral anterior cingulate was associated with more consistent performance. They concluded that these “results indicate that regionally specific components of the fronto-temporal dopaminergic network are functionally involved in working memory performance in humans.”

Journal of Neuroscience

^{18}F -FET PET Enhances MR Spectroscopy in Gliomas

Floeth et al. from the Heinrich-Heine University (Dusseldorf, Germany) reported in the February issue of the *Journal of Neurosurgery* (2005;102:318–327) on a study designed to determine the predictive value of ^{18}F -fluoroethyl-L-tyrosine (^{18}F -FET) PET and MR spectroscopy for tumor diagnosis in patients with suspected gliomas. The study included 50 patients with newly diagnosed intracerebral lesions diagnosed as diffuse gliomas by contrast-enhanced MR. ^{18}F -FET PET and MR spectroscopy analyses were performed on each patient. PET was considered positive with lesion-to-brain ratios of uptake >1.6 . MR spectroscopy was considered positive when N-acetylaspartate was decreased in conjunction with an absolute increase of choline, with a ratio of the previous to the latter ≤ 0.7 . These PET and MR ratios were compared with biopsy findings and were significant independent predictors for correct identification of tumor tissue. Accuracy in such identification could be increased from 68% with the use of MR imaging alone to 97% with the addition of ^{18}F -FET PET. The authors concluded that “in patients with intracerebral lesions supposed to be

diffuse gliomas on MR imaging, ^{18}F -FET PET and MR spectroscopy analyses markedly improved the diagnostic efficacy of targeted biopsies.”

Journal of Neurosurgery

^{18}F -FDOPA PET and the Effects of Aging

In an article e-published ahead of print on February 23 in the *Journal of Cerebral Blood Flow and Metabolism*, Kumakura et al. from the Aarhus University Hospitals and the Centre for Functionally Integrated Neuroscience (Aarhus, Denmark) reported on a study of potential biasing effects in the current use of ^{18}F -fluorodopa (^{18}F -FDOPA) PET to study age-related changes in dopamine release and transport. The authors applied a constrained compartmental analysis to calculate the imaged brain concentrations of the plasma metabolite 3-O-methyl-FDOPA during 120 minutes of ^{18}F -FDOPA circulation in 3 groups of participants: healthy young and healthy elderly individuals and individuals with Parkinson's disease. A global negative bias was found in conventional estimates of ^{18}F -FDOPA clearance when compared with those derived from the novel analysis. In addition, the effective distribution volume for ^{18}F -FDOPA, an index of dopamine storage capacity in brain, was reduced by 85% in the putamen of patients with PD and 58% in healthy elderly participants when compared with healthy young participants. This indicates that the storage capacity for dopamine in both caudate and putamen in patients with PD is more profoundly impaired than is the capacity for ^{18}F -FDOPA utilization as routinely calculated by conventional net influx plots. The authors added that these results “constitute the first demonstration of an abnormality in the cerebral utilization of ^{18}F -FDOPA in caudate and putamen as a function of normal aging, which we attribute to loss of vesicular storage capacity.”

Journal of Cerebral Blood Flow and Metabolism

¹²³I-β-CIT SPECT and Serotonin Transporters

In an article e-published ahead of print on March 16 in *Neuropsychopharmacology*, de Win et al from the University of Amsterdam (The Netherlands) reported on a study validating the use of ¹²³I-β-carbomethoxy-3β(4-iodophenyl)tropane (¹²³I-β-CIT) SPECT to assess 5-HT serotonin transporters (SERTS) in humans. Although ¹²³I-β-CIT has shown promise in imaging of psychiatric diseases by binding in SERT-rich areas of the brain, the authors sought to verify that the technique could be useful in SERT-low cortical areas. The study included 6 healthy men who underwent 2 ¹²³I-β-CIT SPECT scans, 1 after pretreatment with the selective 5-HT reuptake inhibitor citalopram and another after administration of a placebo. Citalopram was found to reduce ¹²³I-β-CIT binding ratios in SERT-rich midbrain and hypothalamus and also (but at much less easily measured levels) in SERT-low cortical areas. Citalopram also increased binding ratios in the dopamine transporter-rich striatum and increased absolute uptake in the cerebellum. The authors concluded that “The results show that ¹²³I-β-CIT SPECT is a valid technique to study SERT binding in vivo in human brain in SERT-rich areas” and that the use of this technique may be valid in SERT-low areas but that such measurements must be interpreted with caution.

Neuropsychopharmacology

^{99m}Tc-HMPAO SPECT and rCBF in Heart Failure

Alves et al. from the University of Sao Paulo Medical School (Brazil) reported in the April issue of the *Journal of Neuroimaging* (2005;15:150–156) on a study using ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) SPECT to assess the presence of resting regional cerebral blood flow (rCBF) abnormalities in patients with heart failure. The study included 17 patients diagnosed to be in New York Heart Association

functional class II or III heart failure and 18 healthy elderly volunteers. Each underwent ^{99m}Tc-HMPAO imaging. The researchers found significant rCBF reductions in 2 main foci in patients with heart failure: the left and right precuneus and cuneus and the right lateral temporoparietal cortex and posterior cingulate gyrus. They also identified a significant correlation between the assessed degree of cognitive impairment in these patients and rCBF reductions. The authors concluded that, “these preliminary findings indicate that posterior cortical areas of the brain may be particularly vulnerable to brain perfusion reductions associated with heart failure and suggest that functional deficits in these regions might be relevant to the pathophysiology of the cognitive impairments” presented by these patients.

Journal of Neuroimaging

Bone Scintigraphy and Marker Levels in Breast Cancer

Begic et al. from the University Clinic Center in Sarajevo (Bosnia and Herzegovina) reported in the February issue of the *Bosnian Journal of Basic Medical Sciences* (2005;5:23–26) on a study designed to correlate levels of the tumor marker Ca 15-3 with indications of bone metastases on bone scintigraphy in women with breast cancer. The study included 25 women with breast cancer who had previously undergone surgical treatment. All patients underwent whole-body scintigraphy, and Ca 15-3 levels were measured. Bone scintigraphy showed bone metastases in 16 (64%) patients. Elevated Ca 15-3 levels were seen in 11 (44%) patients with metastases and 1 patient (4%) with no metastases noted on scintigraphy. Significant differences in Ca 15-3 levels were found in patients with metastases on scintigraphy compared with patients with no metastases. The authors concluded that because “no significant correlation was found between level of Ca

15-3 and number of metastases, we consider scintigraphy an appropriate method for assessment of bone metastases in breast cancer.”

Bosnian Journal of Basic Medical Sciences

Immuno-PET with ¹²⁴I-Labeled Antibody

Robinson et al. from the Fox Chase Cancer Center (Philadelphia, PA) reported in the February 15 issue of *Cancer Research* (2005;65:1471–1478) on a study investigating the potential for engineered antibody fragments in the development of novel PET tracers based on expression of tumor-associated antigens. The study focused on a small engineered ¹²⁴I-labeled antibody fragment specific for the HER2 receptor tyrosine kinase (C6.5 diabody). Working with mouse tumor xenografts, the authors found a time-dependent increase in tumor-to-background signal over the course of the experiments. As part of the experiment, they also validated a method for using a clinical PET/CT scanner to quantify tumor uptake in small-animal model systems. Using this system and the HER2-dependent imaging, quantitation of tumor targeting by PET correlated with traditional necropsy-based analysis at all time points analyzed. They concluded that “diabodies may represent an effective molecular structure for development of novel PET radiotracers.”

Cancer Research

Gated ^{99m}Tc-MIBI SPECT and Regional EF

In the March issue of *Chest* (2005;127:778–786), Lapeyre et al. from the Mayo Clinic and Mayo Foundation (Rochester, MN) reported on a study designed to evaluate a technique for quantitative regional wall motion assessment using gated ^{99m}Tc-sestamibi SPECT. The study included 14 healthy individuals and 25 patients who had experienced myocardial infarction (MI). All patients underwent gated ^{99m}Tc-sestamibi SPECT imaging, with

gated short-axis slice reconstruction and identification of endocardial borders. Regional ejection fraction (EF) and myocardial perfusion were determined for 5 regions within each of 5 selected slices in each study. Ten patients also underwent echocardiographic (ECG) regional wall-motion studies, with results compared with corresponding SPECT slice results. Results indicated high interobserver reproducibility in the assessment of regional EFs. Regional EFs correlated significantly with regional perfusion in anterior walls, lateral walls, and inferior walls. Significant associations between the regional EFs and ECG regional wall motion assessment were found at the base, midventricle, and apex. The authors concluded that, "gated SPECT images obtained with ^{99m}Tc -sestamibi can provide reproducible quantitative, segmental regional EFs for multiple left ventricular slices that are significantly associated with subjective regional wall motion assessment by echocardiography."

Chest

Dual-Isotope ECG-Gated SPECT and Mild CAD

Yoda et al. from the Nihon University School of Medicine (Tokyo, Japan) reported in the March issue of *Circulation Journal* (2005;69:301–305) on a study to determine whether myocardial perfusion SPECT is useful in the diagnosis of mild, single-vessel coronary artery disease (CAD). The study included 97 individuals with a low likelihood of CAD and 46 patients with single-vessel CAD, each of whom underwent separate acquisition, dual-isotope electrocardiograph-gated exercise SPECT. Among the 46 patients with single-vessel disease, 22 were classified as having mild CAD (stenosis = 50%–75%) and 24 as having moderate-to-severe CAD (stenosis \geq 76%). The sensitivity of myocardial perfusion alone was 50% for the mild CAD subgroup and 83% for the moderate-to-severe subgroup. The overall specificity was 90%. When wall motion analysis was added, sensi-

tivity increased to 82% in the mild subgroup and 92% in the moderate-to-severe subgroup. The authors concluded that "the ability to detect a wall motion abnormality immediately after exercise gives incremental diagnostic value to myocardial perfusion SPECT in the identification of mild, single-vessel CAD."

Circulation Journal

Predicting Recovery After Acute Myocardial Infarction

Seki et al. from Gunma University (Maebashi, Japan) reported in the March issue of *Circulation Journal* (2005;69:311–319) on a study comparing the abilities of combinations of ^{99m}Tc -tetrafosmin and ^{123}I - β -methyliodophenyl pentadecanoic acid (BMIPP) SPECT, ^{18}F -FDG PET and ^{123}I -BMIPP SPECT, and ^{18}F -FDG PET and ^{99m}Tc -tetrafosmin SPECT in predicting functional improvement of ischemic myocardium after a large acute myocardial infarction. The study included 10 patients who had experienced large acute myocardial infarction within the past 3 weeks. Each patient underwent ^{99m}Tc -tetrafosmin SPECT, ^{123}I -BMIPP SPECT, and ^{18}F -FDG PET imaging. At 6-month follow-up, all patients had undergone successful revascularization with no restenosis, and follow-up ^{99m}Tc -tetrafosmin SPECT imaging was performed. Researchers scored regional tracer uptake in each of the study images, determined matches and mismatches, and used quantitative gated SPECT to score wall motion. When the relative abilities of combinations of imaging procedures were analyzed, results showed that ^{123}I -BMIPP and ^{99m}Tc -tetrafosmin SPECT imaging sensitivity was 61% in predicting functional improvement, with 94% for ^{18}F -FDG PET and ^{123}I -BMIPP SPECT, and 76% for ^{18}F -FDG PET and ^{99m}Tc -tetrafosmin SPECT. The specificity of ^{123}I -BMIPP and ^{99m}Tc -tetrafosmin SPECT imaging in predicting functional improvement was

83%, with 40% for ^{18}F -FDG PET and ^{123}I -BMIPP SPECT, and 49% for ^{18}F -FDG PET and ^{99m}Tc -tetrafosmin SPECT. The accuracy of the combination of ^{123}I -BMIPP and ^{99m}Tc -tetrafosmin SPECT imaging in predicting functional improvement was 70%, that of ^{18}F -FDG PET and ^{123}I -BMIPP SPECT was 71%, and that of ^{18}F -FDG PET and ^{99m}Tc -tetrafosmin SPECT was 63%. The authors concluded that the combination of ^{123}I -BMIPP and ^{99m}Tc -tetrafosmin SPECT imaging is a practical modality for predicting the functional improvement of ischemic myocardium after a large acute myocardial infarction.

Circulation Journal

Therapy

^{131}I -Labeled Chimeric Tumor Necrosis RIT

In the March 1 issue of the *Journal of Clinical Oncology* (2005;23:1538–1547), Chen et al. from Fudan University (Shanghai, China) reported on a study investigating the therapeutic efficacy and toxicity of ^{131}I -labeled chimeric tumor necrosis radioimmunotherapy (RIT) in patients with advanced lung cancer. Tumor necrosis treatment uses degenerating tumor cells and necrotic regions of tumors as RIT targets. The multiinstitutional study included 107 patients with advanced lung cancer who had experienced previous treatment failure after a median of 3 radio- or chemotherapy regimens. All patients underwent systemic or intratumoral injection of ^{131}I -chimeric tumor necrosis antibody. Results showed an objective response rate of 34.6% (complete response, 3.7%; partial response, 30.8%; no change, 55.1%; progressive disease, 10.3%) in all patients and 33% in patients with non-small cell lung cancer. Biodistribution studies showed excellent localization of radioactivity in tumors in both systemically and intratumorally injected patients. The authors concluded that RIT with ^{131}I -

chimeric tumor necrosis antibody was “well tolerated and can be used systemically or locally to treat refractory tumors of the lung.”

Journal of Clinical Oncology

LundADose Method for Absorbed Dose Assessment in Therapy

In an article published in the February issue of *Cancer Biotherapy and Radiopharmaceuticals* (2005;20:92–97), Sjogreen et al. from Lund University (Sweden) described a new method for absorbed-dose assessment in radionuclide therapy. The method is based on activity quantification by a conjugate-view methodology that is applied to serial whole-body, anterior–posterior, scintillation camera scans. The method includes separate corrections for attenuation, scatter, and overlapping organs. Additional development includes accommodation of the capabilities of

dual-head camera systems with built-in anatomical imaging. Time–activity data are included, along with dosimetric calculations based on the model of the Medical Internal Radiation Dose committee. The “LundADose” program enables automatic quantification, image registration, and absorbed dose calculations for larger numbers of patient studies. The method was evaluated in performance of whole-body activity quantification for patients undergoing radioimmunotherapy with ^{111}In - or ^{90}Y -labeled monoclonal.

Cancer Biotherapy and Radiopharmaceuticals

^{123}I -Rituximab Imaging of CNS Lymphomas

Dietlein et al. from the University of Cologne (Germany) reported in the April issue of the *European Journal of Haematology* (2005;74:348–352) on dosimetric measurements of

systemically administered intravenous ^{123}I -labeled rituximab to evaluate uptake in primary central nervous system lymphoma (PCNSL). The study included 4 patients with PCNSL who received a preinfusion of rituximab followed by 200–500 MBq ^{123}I -rituximab. SPECT imaging was performed at 1, 24, and 48 hours after administration of the radiolabeled compound. One patient showed very weak uptake of ^{123}I -rituximab into tumor tissue, with uptake 9-fold lower than blood-pool accumulation. The authors concluded that these data suggest that systemic monoclonal antibody–based radioimmunotherapy is not feasible in patients with PCNSL, because a sufficient activity delivered to tumor would be associated with severe hemotoxicity. They noted that whether “an uptake of therapeutic rituximab doses into PCNSL can be achieved remains questionable.”

European Journal of Haematology

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nonprescription drug and in January approved the Fleming pediatric product.

Department of Health and Human Services

MDS and AECL Announce Mediation for MAPLE Project

MDS Inc. and Atomic Energy of Canada Limited (AECL) announced on March 11 that the 2 companies had reached an agreement to seek a mediated resolution of issues related to the construction, commissioning, and operation of the MAPLE facilities in Chalk River, Ontario. Ontario Appeals Court Judge Stephen Goudge has been

appointed as the mediator and will work closely with the 2 parties. The Government of Canada has agreed to have a representative as a formal observer in this process. Robert Van Adel, President and Chief Executive Officer of AECL added, “We are entering into this voluntary mediation process with the spirit and intent of arriving at a satisfactory resolution to all of the outstanding issues, and we look forward to the successful commissioning of the MAPLE reactors.”

Atomic Energy of Canada Limited

Donut Stop Delays Radionuclide Delivery

On March 10, *The Pawtucket (RI) Times* reported that a truck

containing $^{99\text{m}}\text{Tc}$ destined for stress testing at a local hospital had been stolen outside a Dunkin’ Donuts store in Seekonk, MA. The driver left the truck running while in the store. Police immediately entered the pickup truck’s information into a national computer alert system, and a regional broadcast was issued to all area police departments about the potentially hazardous material. The vehicle was found later in the day, with the radionuclide vials intact and unopened. The thief was unaware of the nature of the cargo, contained in a small “ammo” box in the truck’s cab.

The Pawtucket (RI) Times