



Each month the editor of *Newsline* selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Many selections come from outside the standard canon of nuclear medicine and radiology journals. Note that although we have divided the articles into therapeutic and diagnostic 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.

Diagnosis

SPECT and MR in Nanoformulated Drug Delivery

In an article e-published ahead of print on August 14 in the *Journal of Leukocyte Biology*, Gorantla and researchers from the University of Nebraska Medical Center (Omaha), Creighton University (Omaha, NE), and Baxter Healthcare Corp. (Round Lake, IL) reported on the potential for quantitative MR and SPECT imaging of macrophage tissue migration in nanoformulated drug delivery. This work is part of continued interest by this group in the development of a macrophage-based nanoparticle system for antiretroviral (ART) drug delivery. Taking as their hypothesis that the same mononuclear phagocytes, bone marrow and blood monocytes, tissue macrophages, microglia, and dendritic cells that serve as targets, reservoirs, and vehicles for HIV dissemination can be used as vehicles for ART, the authors reported on blood marrow macrophages as carriers

for nanoparticle-formulated indinavir. SPECT, T2-weighted MR imaging, gamma scintillation spectrometry, and histology provided quantitative metrics. The study was conducted in a drug-naïve mouse model, in which bone marrow macrophages labeled with super paramagnetic iron oxide and/or ^{111}In -oxine were injected. Kinetics were observed over 14 days. SPECT and MR imaging indicated that bone marrow macrophage densities were significantly greater in the liver and spleen than in other tissues or organs. Transfer of bone marrow macrophages loaded with nanoparticle-formulated indinavir produced drug levels in lymphoid and nonlymphoid tissues that exceeded reported therapeutic concentrations by 200- to 350-fold on day 1 and remained in excess of 100- to 300-fold on day 14. The authors concluded that “these data show real-time kinetics and destinations of macrophage trafficking and demonstrate the feasibility of monitoring macrophage-based, nanoformulated ART.”

Journal of Leukocyte Biology

$^{99\text{m}}\text{Tc}$ -GSA SPECT in Acute Hepatic Damage

Togashi et al. from the Yamagata University (Japan) reported on August 18 ahead of print in *Hepatology Research* on a study designed to clarify the clinical significance of the asialoglycoprotein receptor (ASGPR) in the human liver in acute hepatitis and fulminant hepatic failure. The study included 18 healthy individuals, 42 patients with acute hepatitis, and 10 patients with fulminant hepatic failure. All underwent $^{99\text{m}}\text{Tc}$ -galactosyl human serum albumin SPECT imaging, with ASGPR expression analyzed separately in the right and left hepatic lobes using indices developed by the authors for this and similar studies. Mean uptake ratio and uptake density values for the whole liver and each

lobe decreased in accordance with the severity of acute hepatic damage. In patients with fulminant hepatic failure, reduction in these values was greater in right than left lobes. Overall, these values for the whole liver correlated well with hepatic functional reserve and total bilirubin levels, and a smaller time-course study indicated that expression of ASGPRs in the right lobe recovered faster than in the left. The authors concluded that this technique “is a clinically useful and reliable indicator for assessing the severity of regional hepatic damage and evaluating regional liver regeneration.”

Hepatology Research

PET Models of Brain Drug Concentrations

In an article e-published on August 8 ahead of print in the *European Journal of Clinical Pharmacology*, Syvanen et al. from Uppsala Imanet (Sweden) reported on a study designed to use PET in combination with venous blood sampling and an arteriovenous transform to predict and model brain drug kinetics. They applied their modeling procedure to data from a clinical PET study in which both arterial and plasma sampling had been performed in parallel with PET measurement of radiolabeled pharmaceutical kinetics in the brain. Predictions of kinetics based on an arterial input were compared with those based on a venous input, each calculated with and without an arteriovenous transform. The authors found that venous-based models for brain distribution using the arteriovenous transform performed as well as models based on arterial data and better than venous-based models without the transform. In addition, the kinetics of 3 different brain regions could be adequately modeled with a common arteriovenous transform and an individual brain distribution model. The

(Continued on page 30N)

(Continued from page 28N)

authors noted that the successes of these investigations indicate that the model can be used “for the calculation of brain kinetics resulting from an arbitrary administration mode by applying this model on venous plasma pharmacokinetics.” They added that this would carry a distinct advantage “in the development of drugs acting in the brain” and in other circumstances in which the effect is likely to be more closely related to the brain than to plasma concentration.

*European Journal of
Clinical Pharmacology*

PET and Islet Graft Survival

Lu et al. from the University of California, Los Angeles, reported in the July 25 issue of the *Proceedings of the National Academy of Sciences USA* (2006;103:11294–11299) on the use of PET in the noninvasive quantitative assessment of islet graft survival. Although islet transplantation is a promising therapeutic approach in patients with type 1 diabetes, both continuing graft function and graft rejection are difficult to monitor. The authors engineered a recombinant adenovirus that targeted isolated islets to express a PET-positive reporter gene. These engineered islets were then transplanted into a mouse model and imaged using microPET. They found that the magnitude of signal on PET was directly related to the transplanted islet mass. In addition, studies in which transplanted islets were dispersed throughout the liver found that clear signals from the liver region of PET reporter-expressing islets were detectable for several weeks. Additional studies indicated that transduction, PET reporter expression, and repeated microPET imaging had no apparent deleterious effects on islet function after implantation. These studies show promise in providing a foundation for exploring noninvasive imaging in patients with type 1 diabetes who undergo islet transplantation to restore glucose homeostasis.

*Proceedings of the National
Academy of Sciences USA*

SPECT and Coronary Atherosclerosis in Hemodialysis

Hase et al. from Toho University Ohashi Hospital (Tokyo, Japan) reported in the August issue of *Therapeutic Apheresis and Dialysis* (2006; 10:321–327) on a study using ^{201}Tl SPECT to determine possible risk factors for progression of coronary atherosclerosis in patients undergoing hemodialysis. The study included 77 patients on hemodialysis who underwent pharmacologic challenge myocardial perfusion imaging with ^{201}Tl SPECT with high-dose adenosine triphosphate. Myocardial perfusion effects were found in 36 patients. Participants were followed for 2 years. Seventy-eight percent of patients with perfusion defects experienced cardiac events during the follow-up period, whereas only 15% of those without such defects experienced events. Cutoff values of plasma concentrations of C-reactive protein were devised to yield positive and negative values for the prediction of coronary events of 65% and 74%, respectively. The authors concluded that both myocardial perfusion SPECT and routine measurement of plasma concentration of C-reactive protein might be useful for prediction of coronary atherosclerosis progression in patients undergoing hemodialysis.

Therapeutic Apheresis and Dialysis

Dopamine Receptor Binding in Epilepsy

In a study published in the August issue of *Epilepsia* (2006;47:1392–1399), Werhahn et al. from the Johannes Gutenberg University (Rhineland-Palatinate, Germany) reported on an ^{18}F -fallypride PET study of dopamine D2/D3 receptor binding in human focal epilepsy. The study included 7 patients with temporal lobe epilepsy and 9 age-matched volunteers. All patients underwent MR imaging, interictal and ictal video electroencephalography, and ^{18}F -FDG, and epilepsy was determined on histology to be the result of hippocampal sclerosis in all.

All participants then underwent ^{18}F -fallypride imaging. The authors calculated binding potentials using a simplified reference tissue and compared epileptogenic regions of interest with those in the unaffected hemisphere in each patient and with binding in healthy participants. They found that ^{18}F -fallypride binding was significantly decreased in the epileptogenic temporal lobe in all patients, a decrease that was especially evident in areas surrounding the seizure-onset zone at the pole and lateral aspects of the temporal lobe. Although the hippocampus uptake of ^{18}F -FDG and hippocampal MR volumes were also significantly reduced, no significant decrease of ^{18}F -FP binding was found in these areas. The authors concluded that these results indicate that the epileptogenic temporal lobe might correspond to “the ‘irritative zone,’” indicating that D2/D3 receptors might play a specific role in the pathophysiology of mesial temporal lobe epilepsy.”

Epilepsia

PET Aids in AD Gene Identification

Theuns et al. from the Flanders Interuniversity Institute for Biotechnology and the University of Antwerp (Belgium) reported in the September issue of *Human Mutation* (2006; 27:888–896) on the identification of a novel mutation in the amyloid precursor protein (APP) gene associated with early onset of Alzheimer’s disease (AD). The group has reported in previous publications on genetic variability in the APP promoter and have expanded perspectives on the various missense mutations that have been described. In this study, in addition to identifying and locating the mutation in a patient with familial early onset AD, they verified in vitro expression of increased A β 42 and decreased A β 40 levels, resulting in a nearly 3-fold increase in the normal A β 42/A β 40 ratio. The patient then underwent PET imaging which revealed “significantly increased cortical

amyloid deposits, supporting that in humans this novel APP mutation is likely causing disease.”

The same research group, this time with Brouwers as first author, also reported on August 24 ahead of print in *Brain* on a study of APP variability in 750 patients with AD (mean age at onset, 75.0 ± 8.6 years). Three different APP promoter mutations were identified in 7 patients, and the authors explored the relationship of these mutations to age of onset and to familial history of dementia. They concluded that their evidence suggests that “mutations in APP regulatory sequences are more frequent than APP coding mutations, and that increased APP transcriptional activity constitutes a risk factor for AD with onset ages inversely correlated with levels of APP expression.”

Human Mutation

Brain

PET Reveals Receptor “Saturation” in Smokers

In the same month that a widely publicized study reported that the amount of nicotine in cigarettes had risen by 10%–30% in the past decade, researchers from the University of California, Los Angeles, described results indicating that cigarette smoking saturates brain $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChRs) in individuals who are tobacco dependent. Brody et al. published their report in the August issue of the *Archives of General Psychiatry* (2006;63:907–915). The study included 11 tobacco-dependent smokers who underwent 2- ^{18}F -fluoro-3-2S-azetidinylmethoxy pyridine (^{18}F -2FA) PET imaging in 14 sessions, each with varying tobacco use, from none to satiety (2.5–3 cigarettes). The authors found that smoking only 1–2 puffs of a cigarette resulted in 50% occupancy of $\alpha 4\beta 2$ nAChRs for >3 hours. Smoking 1 or more cigarettes resulted in >88% receptor occupancy. The authors concluded that “cigarette smoking in amounts used by typical daily smokers leads to nearly complete occupancy of $\alpha 4\beta 2$ nAChRs,” indi-

cating that tobacco-dependent smokers maintain this saturation throughout the day. They added that because $\alpha 4\beta 2$ nAChRs are desensitized after prolonged binding to nicotine, the extent of receptor occupancy found in this study “suggests that smoking may lead to withdrawal alleviation by maintaining nAChRs in the desensitized state.”

Archives of General Psychiatry

Panic Disorder Treatment Imaged

In an article e-published ahead of print on August 2 in *Neuroimage*, Sakai and colleagues from a consortium of Japanese hospitals and universities reported on ^{18}F -FDG PET imaging to elucidate the mechanisms by which cognitive-behavioral therapy improves symptoms in individuals with panic disorder. The study included 12 patients who showed improvement in panic disorder after cognitive-behavioral therapy and who underwent ^{18}F -FDG PET brain imaging both before and after therapy. In 11 of these 12 patients, decreased glucose utilization was seen in the right hippocampus, left anterior cingulate, left cerebellum, and pons, and increased glucose utilization was seen in the bilateral medial prefrontal cortices. The authors noted significant correlations between these findings and scores on the Panic Disorder Severity Scale and numbers of panic attacks preceding each scan. They concluded that “the completion of successful cognitive-behavioral therapy involved not only reduction of the baseline hyperactivity in several brain areas but also adaptive metabolic changes of the bilateral medial prefrontal cortices in panic disorder patients.”

Neuroimage

^{11}C -Flumazenil PET Gene Mutation Studies in Epilepsy

Fedi et al. from Austin Health Heidelberg (Victoria, Australia) reported on July 26 ahead of print in *Neuroimage* on a study using ^{11}C -

flumazenil PET to explore newly discovered single-gene mutations causing human epilepsy. The authors tested the hypothesis that individuals affected by the GABRG2(R43Q) mutation associated with familial generalized epilepsy have reduced binding to the GABA(A) receptor complex as assessed by ^{11}C -flumazenil PET. The study included 14 individuals with the targeted mutation and 20 healthy individuals, each of whom underwent PET imaging. Receptor binding in individuals with the mutation was reduced compared with that in controls. The greatest reductions were found to be in the insular and anterior cingulate cortices. In addition to providing in vivo evidence of reduced benzodiazepine receptor binding in individuals with this mutation, the authors concluded that these findings “are likely to represent an important clue to the mechanisms linking this gene defect and the epilepsy phenotype.”

Neuroimage

PET Illuminates Predisposition to Cocaine Addiction

Nader et al. from the Wake Forest School of Medicine (Winston-Salem, NC) reported in the August 9 issue of *Nature Neurosciences* (2006;9:1050–1056) on a study using PET in rhesus macaques to determine whether dopamine D2 receptor availability is associated with the rate of cocaine reinforcement and to study changes in brain dopaminergic function during maintenance of and abstinence from cocaine. The study included 12 monkeys that were allowed to self-administer cocaine. Serial PET imaging indicated that baseline D2 receptor availability was negatively correlated with rates of cocaine self-administration. D2 receptor availability decreased by 15%–20% within 1 week of initiating self-administration and remained reduced by approximately 20% during 1 year of exposure. Long-term reductions in D2 receptor persisted for up to 1 year of abstinence in some monkeys. The authors concluded that these data

“provide evidence for a predisposition to self-administer cocaine based on D2 receptor availability and demonstrate that the brain dopamine system responds rapidly following cocaine exposure.” Individual differences in the rate of recovery of D2 receptor function during abstinence were noted. They added that “The present findings also suggest that more vulnerable individuals are even more likely to continue using cocaine because of the cocaine-induced reductions in D2 receptor levels.” The article was covered in numerous media outlets.

Nature Neurosciences

PET in Pediatric and Young Adult Bone Sarcoma

Kneisl et al. from the Carolinas Medical Center (Charlotte, NC) reported on July 27 ahead of print in *Clinical Orthopaedics and Related Research* on the use of ^{18}F -FDG PET to detect occult nonpulmonary metastases in young patients newly diagnosed with either Ewing’s sarcoma or osteosarcoma. The retrospective study included data from 55 patients who were younger than 30 years old at initial imaging. PET detected metastases in 12 (22%) of these patients, 8 of whom (67%) had disease outside the lung. Only 4 (7%; 3 [18% of] patients with Ewing’s sarcoma and 1 [3% of] patient with osteosarcoma) were upstaged to stage IV solely as a result of PET findings. In patients with Ewing’s sarcoma, the most important alteration in treatment decision was the substitution of radiation for surgery for local control.

Clinical Orthopaedics and Related Research

PET vs. Scintigraphy in ^{131}I -Negative Thyroid Cancer

In an article e-published on August 8 ahead of print in the *Journal of Clinical Endocrinology and Metabolism*, Rodrigues et al. from the Hietzing Hospital and the Medical University of Vienna (Austria) reported on a comparison of $^{99\text{m}}\text{Tc}$ -depreotide scintigraphy and ^{18}F -FDG PET in the

diagnosis of radioiodine-negative thyroid cancer. The study included 10 radioiodine-negative patients with suspected recurrent or metastatic thyroid cancer who were imaged with both $^{99\text{m}}\text{Tc}$ -depreotide scintigraphy and ^{18}F -FDG PET. Scintigraphy and PET provided true-positive results in 9 (90%) and 7 (70%) patients, respectively. In 3 patients, scintigraphy was better than PET in detecting recurrent or metastatic disease, whereas PET identified metastatic disease not seen on scintigraphy in only 1 patient. The authors concluded that these results indicate the potential value of $^{99\text{m}}\text{Tc}$ -depreotide scintigraphy “for the diagnosis of thyroid cancer in the setting of detectable thyroglobulin and negative radioiodine scan.” They added that scintigraphy in this setting “adds complementary information regarding the somatostatin receptor status of lesions, which may be helpful for individual therapy planning in this group of patients which are hard to manage clinically.”

Journal of Clinical Endocrinology and Metabolism

Scintigraphy in ^{131}I -Negative Thyroid Cancer

Valsamaki et al. from the Alexandra University Hospital (Athens, Greece) reported in the August 15 issue of the *International Journal of Cancer* (2006; 119:968–970) on a case study evaluating $^{99\text{m}}\text{Tc}$ -depreotide scintigraphy in the restaging of papillary thyroid carcinoma with detectable serum thyroglobulin levels and negative ^{131}I whole-body scan. The patient was a 68-year-old man with stage 3 papillary thyroid cancer, recent negative ^{131}I whole-body scan, and a mild increase in serum thyroglobulin. The patient underwent $^{99\text{m}}\text{Tc}$ -depreotide whole-body planar and cervicothoracic scintigraphy, and results were compared with findings from ultrasound and CT studies and from nodal neck dissection and histopathology. $^{99\text{m}}\text{Tc}$ -depreotide scintigraphy identified cervical lymph node metastases that did not accumulate radioiodine,

findings that were confirmed on ultrasound, CT, and histopathology. In addition, lymph node immunoreactivity was positive for somatostatin receptor subtypes 2, 5, and 3. The authors concluded that “scintigraphy with $^{99\text{m}}\text{Tc}$ -depreotide could prove a useful adjunct to the armamentarium for the follow-up of papillary thyroid cancer, especially in the setting of detectable serum thyroglobulin and negative ^{131}I whole-body scan.”

International Journal of Cancer

Therapy

^{211}At -Labeled mAb in CD25-Expressing Leukemias

Zhang et al. from the National Institutes of Health reported in the August 15 issue of *Cancer Research* (2006;66:8227–8232) on the evaluation of a ^{211}At -labeled anti-CD25 monoclonal antibody (mAb) as a potential radioimmunotherapy agent for CD25-expressing leukemias and lymphomas. Studies were performed in severe combined immunodeficient/nonobese diabetic mice bearing the karpas299 leukemia and in nude mice bearing the SUDHL-1 lymphoma. Pharmacokinetic investigations indicated that clearance and biodistribution of the ^{211}At -labeled mAb were quite similar to those for the same mAb labeled with ^{125}I (with the exception of higher stomach uptake of the ^{211}At). Therapy using 15 μCi of the ^{211}At -labeled mAb prolonged survival of the leukemia-bearing mice significantly when compared with untreated mice and with mice treated with a ^{211}At -labeled non-specific control antibody. By day 46 after initiation of the study, all of the mice in the control and control antibody groups had died, but >70% of mice in the ^{211}At -labeled mAb-treated group were still alive. The authors conclude that these data point toward “an effective therapeutic agent for patients with CD25-expressing leukemias.”

Cancer Research
(Continued on page 36N)

(Continued from page 32N)

¹⁸⁸Re-Labeled Pretargeting

Liu et al. from the University of Massachusetts Medical School (Worcester) and the University of Oklahoma Health Sciences Center (Oklahoma City) reported in the August 15 issue of *Clinical Cancer Research* (2006;12:4958–4964) on a study of ¹⁸⁸Re-radiolabeled pretargeting for more effective drug delivery in

radiotherapy. This article is a follow-up to original work in which the authors proposed the Watson–Crick pairing of phosphorodiamidate morpholino oligomers (MORF) as a recognition system in tumor pretargeting and initial studies using MORF pretargeting with ^{99m}Tc as the radiolabel. In the current study, mice injected with ¹⁸⁸Re-labeled MORF showed rapid tumor localization of tracer and rapid clearance from normal tissues. Tumor growth in the study group

ceased 1 day after injection, whereas tumors continued to grow at a constant rate among the 3 different control groups. Average net tumor weights were also significantly lower in the treatment than the control groups at day 5, when the mice were killed and results analyzed. The authors concluded that “MORF pretargeting has now been shown to be a promising approach for tumor radiotherapy as well as diagnosis.”

Clinical Cancer Research

(Continued from page 14N)

offer demonstrations, and answer questions. This provides a new opportunity to present this excellent work at the SNM Annual Meeting. I hope that many members of the nuclear medicine community will consider participating in this novel effort.

(2) We will also designate a classroom in which educational and informational programs on information science and technology will be offered throughout the meeting. These programs may be specific to our field or of more general interest. For example, a representative of the Integrating the Healthcare Enterprise initiative may discuss the development of guidelines for the more effective display of nuclear medicine image data within a PACS environment. Another individual might present different approaches to comparing a patient's ¹⁸F-FDG PET brain scan with a normalized database. Because we will be in Washington, DC, it might be useful to invite a representative

from the National Library of Medicine to show us how to perform more directed and efficient PubMed literature searches.

Both of these components of the InfoSNM program will be located in the same meeting area, with a partition that can be pulled to separate them if necessary. This area will be well marked and should be easy to find. I am very excited about this new program. Although it may begin slowly, I hope it will continue to grow in the years to come. If you have questions, please feel free to contact me at frederic.fahey@childrens.harvard.edu (617-355-2809), other members of the InfoSNM Committee (Jim Halama, Marie Kijewski, and Jerry Wallis), or Lynn Barnes, director of education at the SNM (lbarnes@snm.org). I look forward to seeing all of you in the InfoSNM area next June in Washington, DC!

*Frederic H. Fahey DSc
Chair, SNM Scientific Program Committee*

(Continued from page 26N)

is included in the *Federal Register* notice.

To submit electronic comments, visit www.fda.gov/dockets/ecomments. Written comments may be sent to: Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD, 20852. Comments must be received by November 9 and include the docket number 2006N-0292.

U.S. Food and Drug Administration

PET in Court

The nuclear medicine community watched with interest in August as PET imaging was used as part of the defense strategy in an appeal on behalf

of a convicted murderer in Georgetown County, SC. Lawyers for Stephen Stanko, an inmate on death row at Lieber Correctional Institution in Ridgeville, filed an appeal on August 21 indicating that PET imaging showed brain damage. The basis of the appeal, which will go to the South Carolina Supreme Court, is that Stanko's execution would be unconstitutional because he has brain damage and could not control his actions. The filing came at the same time that state prosecutors announced their intention to seek a second death penalty for Stanko in another killing. The defendant's lawyer told the press that the initial introduction of PET in the defendant's first trial “was a precedent-setting case.... We're opening our

eyes to why people do these things. He [Stanko] has a brain defect from birth. He has 50%–80% loss of function in the frontal lobe and that translates into lack of character.” The appeal may take up to 1 year.

Prosecutors and most medical observers were skeptical of the attorney's remarks and of the relevance of PET results in this case. However, the case—and the public interest generated—are reminders that as nuclear medicine procedures continue to explore verifiable measures of brain function in addiction, schizophrenia, and a range of dementias, nuclear medicine experts will be more frequently called upon to interpret the results of imaging in the legal setting.

Myrtle Beach Online