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 recently 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 both 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. In this month's briefs, for example, the articles reviewed in the "Therapy" section include nuclear imaging techniques used to assess the effectiveness of nonradioisotopic therapies.

DIAGNOSIS

^{123}I-FP-CIT SPECT Imaging in Dementia Differentiation

McKeith et al. from Newcastle University (Newcastle upon Tyne, UK) reported in the April issue of *Lancet Neurology* (2007;6:305–313) on a phase III multicenter study of the sensitivity and specificity of ^{123}I-FP-CIT SPECT dopamine transporter (DAT) imaging in dementia with Lewy bodies (DLB). The study included 326 patients with diagnoses of probable or possible DLB (n = 94 and 57, respectively), non-DLB dementia (n =147), or no diagnosis (n = 28) who underwent SPECT imaging. Experienced physicians unaware of referring diagnoses assessed the resulting images as normal or abnormal for DAT uptake in the basal ganglia (the latter has been identified by the International Consensus Criteria for DLB as a suggestive diagnostic feature). The authors found that of those scans judged to be abnormal, 77.7% correlated with diagnoses of clinically probable DLB, with a specificity of 90.4% for excluding non-DLB dementia. Overall diagnostic accuracy was 85.7%, and positive and negative predictive values were 82.4% and 87.5%, respectively. They concluded that these findings "confirm the high correlation between abnormal (low binding) DAT activity measured with ^{123}I-FP-CIT SPECT and a clinical diagnosis of probable DLB" and that the resulting diagnostic accuracy is "sufficiently high for this technique to be clinically useful in distinguishing DLB from Alzheimer's disease." Differentiation between these types of dementias is especially important given the significant differences in patient management and outcomes.

Lancet Neurology

PET and Pediatric Hodgkin's Relapse

In the April issue of *Pediatric Blood and Cancer* (2007;48:399–402), Meany et al. from Children's National Medical Center (Washington, DC) reported on a study assessing the effectiveness of PET in predicting disease relapse in pediatric patients with Hodgkin's lymphoma. The study included 23 patients with the disease who underwent PET imaging either at diagnosis or in early treatment and again after completion of therapy and at follow-up. At the completion of therapy, PET scans were negative in 22 of 23 patients, but follow-up PET proved to be positive in 10 of these patients (for a total of 11 patients with positive posttherapy scans). Of these 11 patients, 5 underwent tissue biopsy that confirmed relapse in 2, 4 showed no abnormal uptake on repeat PET, and 2 had persistently positive but stable scan findings with no relapse at the time of article submission. Twelve (52.2%) of the original 23 patients had consistently negative PET scans with no relapse over the follow-up period. The authors concluded that although PET is a sensitive (100%) method for evaluating pediatric patients after treatment for Hodgkin's lymphoma, it is not specific (57.1%; strong negative predictive value [100%], poor positive predictive value [18.2%]). They cautioned against making treatment decisions based solely on PET findings in similar patient groups.

Pediatric Blood and Cancer

^{11}C-Raclopride PET and Conditioned Dopamine Release

Boileau et al. from the Montreal Neurological Institute (Quebec) reported in the April issue of the *Journal of Neuroscience* (2007;27:3998–4003) on an ^{11}C-raclopride PET study investigating whether amphetamine-predictive stimuli (i.e., cues) can stimulate striatal dopamine release in humans. Previous studies in small animals have suggested that neutral stimuli repeatedly paired with the administration of drugs of abuse can initiate striatal dopamine release even in the absence of drug administration, a response that may be involved in drug seeking and craving. The study included 9 healthy male volunteers, each of whom was administered a capsule containing amphetamine tablets (0.3 mg/kg) every other day for a total of 3 administrations in the scanner suite. After at least 2 weeks, a placebo of identical appearance was substituted for the amphetamine and administered in the same manner and in the same environment. Each volunteer underwent ^{11}C-raclopride PET imaging after the first amphetamine administration, after placebo administration, and during a control scan with

no pill. Using the control scan as a baseline, tracer binding to dopamine D_2 and D_3 receptors was decreased by 22% in the ventral striatum and 11% in the putamen after amphetamine administration. These decreases were also seen in placebo administration, with the decrease in binding potential in the ventral striatum (23%) actually slightly exceeding that with amphetamine. The authors concluded that "these results suggest that cues associated with amphetamine increase dopamine transmission, providing evidence that this system is involved in reward prediction in humans."

Journal of Neuroscience

PET and Cocaine Dependence and Relapse

In another ^{11}C-raclopride PET study of the role of dopamine release in substance abuse and dependence, Martinez et al. from the New York State Psychiatric Institute (New York) reported in the April issue of the *American Journal of Psychiatry* (2007;164:622–629) on an investigation designed to characterize pre- and postsynaptic dopamine function in recently detoxified cocaine-dependent individuals. The study included 24 cocaine-dependent and 24 matched healthy participants who underwent ^{11}C-raclopride PET baseline imaging and were imaged again after intravenous amphetamine administration. Dopamine response to this acute amphetamine challenge was assessed in striatal subregions. Cocaine-dependent participants then underwent a laboratory model of relapse, consisting of a priming dose of cocaine followed by the choice of self-administration of subsequent cocaine doses or a monetary reward. PET imaging showed that cocaine dependence was associated with a marked reduction in amphetamine-induced dopamine release in the functional subregions of the striatum. Findings of significantly reduced dopamine transmission in the ventral striatum and anterior caudate were predictive of the choice for cocaine over money. The authors concluded that "cocaine dependence is associated with impairment of dopamine function, and this impairment appears to play a critical role in relapse."

American Journal of Psychiatry

PET Shows Brain Loci of Arthritic Pain Processing

In an article e-published in the March 28 issue of *Arthritis and Rheumatism (*2007;56:1345–1354), Kulkarni et al. from the University of Manchester Rheumatic Diseases Centre and Hope Hospital (Salford, UK) reported on a study using ^{18}F-FDG PET to compare brain areas involved in processing arthritic pain and experimental pain in a group of individuals with osteoarthritis. The study included 12 patients with knee osteoarthritis who underwent PET imaging of the brain while experiencing 3 different pain states: no pain (control), arthritic knee pain, and experimentally induced knee pain. The authors found that although both types of pain activated the "pain matrix," the parallel networks of brain structures previously identified by functional neuroimaging as responsive to experimentally induced acute pain, only the arthritic pain was associated with significantly increased activity in the cingulate cortex, thalamus, and amygdala—areas involved in processing of fear, emotion, and aversive conditioning. They concluded that these findings suggest that "studies of experimental pain provide a relevant but quantitatively incomplete picture of brain activity during arthritic pain" and that "the search for new analgesics for arthritis that act on the brain should focus on drugs that modify this circuitry."

Arthritis and Rheumatism

SPECT in Alzheimer Gender Differences

Moran et al. from the Massachusetts General Hospital (Boston, MA) reported on April 2 ahead of print in *Neurobiology of Aging* on a study using perfusion SPECT and abnormal regional cerebral function to investigate gender differences in the presence of psychotic symptoms in patients with Alzheimer's disease (AD). The study included an age- and dementia severity-consistent group of 51 AD patients with and 53 AD patients without psychotic symptoms. The authors found that perfusion was lower in female patients with psychotic symptoms in right inferolateral prefrontal cortex and in inferior temporal regions than in female patients without such symptoms. Perfusion was higher in male patients with psychotic symptoms in the right striatum than in male patients without such symptoms. They concluded that "these results support the role of right hemisphere prefrontal and lateral temporal cortex in the psychosis of AD in women but not in men and raise the possibility that these dysfunctional processes have a gender-specific regional pathophysiology in AD."

Neurobiology of Aging

PET and Carotid Inflammation

Tahara et al. from the Kurume University School of Medicine (Japan) reported in the April 10 issue of the *Journal of the American College of Cardiology* (2007;49:1533–1539) on a study of the relationship of vascular inflammation as detected by ^{18}F-FDG PET with metabolic syndrome, the group of coexisting metabolic factors that increase individual risk of coronary artery disease, stroke, peripheral vascular disease, and type 2 diabetes. The study included 216 patients who underwent PET imaging for cancer screening. Standard uptake values (SUVs) of tracer in the carotid artery were used to assess vascular inflammation in carotid atherosclerosis. These SUVs were found to be directly correlated with waist circumference, hypertensive medication, carotid intima-media thickness, high-density lipoprotein cholesterol, the homeostasis model assessment of insulin resistance, and high sensitivity C-reactive protein. Age- and gender-adjusted SUVs were significantly related to the aggregate number of these components of the metabolic syndrome. The authors concluded that "the metabolic syndrome is associated with inflammation in carotid

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atherosclerosis" and that routine PET imaging may be a useful screening tool in assessment and management.

Journal of the American College of Cardiology

^{18}F-FMT and ^{18}F-FDG PET in Sarcoidosis

Kaira et al. from the Gunma University Graduate School of Medicine (Japan) reported in the April issue of *Chest* (2007;131:1019–1027) on a study investigating the utility of L-3-^{18}F-α-methyltyrosine (^{18}F-FMT) PET in combination with ^{18}F-FDG PET in distinguishing sarcoidosis from malignancy. The study included 24 patients with sarcoidosis who were referred for suspected malignancy and who underwent both ^{18}F-FMT and ^{18}F-FDG PET imaging. The study group included 17 patients with extrapulmonary manifestation mimicking malignant disease, 3 patients with bilateral hilar lymphadenopathy, and 4 patients with multiple nodules mimicking pulmonary metastasis. All extranodal lesions (liver, spleen, and bone) and lymphadenopathies that were visually positive on ^{18}F-FDG PET were negative on ^{18}F-FMT PET. No malignancies were confirmed in this patient group. However, in a control group of patients with lung cancer, standard uptake values were much higher for ^{18}F-FDG than for ^{18}F-FMT. The authors concluded that because ^{18}F-FDG PET could not differentiate sarcoidosis from malignant disease in their original study group, use of "^{18}F-FMT PET in combination with ^{18}F-FDG PET may be the effective method to distinguish sarcoidosis from malignancy."

Chest

^{18}F-Choline or ^{11}C-Acetate PET/CT in Residual Prostate Cancer

In an article e-published on April 8 ahead of print in *BJU International,* Vees et al. from University Hospital Geneva (Switzerland) reported on a study assessing the value of ^{18}F-choline or ^{11}C-acetate PET/CT in detecting residual or recurrent tumor after radical prostatectomy in patients with very low prostate-specific antigen (PSA) levels (<1 ng/mL) referred for adjuvant or salvage radiotherapy. The study included 20 such consecutive patients with a median PSA of 0.33 ng/mL, 9 of whom underwent ^{18}F-choline PET/CT, 9 of whom underwent ^{11}C-acetate PET/CT, and 2 of whom underwent both types of imaging. Eighteen patients also underwent endorectal coil MR imaging. Abnormal local tracer uptake was seen in 5 patients in the ^{18}F-choline imaging group and 6 patients in the ^{11}C-acetate imaging group, with no uptake in the 2 patients who underwent imaging with both tracers. Only a single potential site of metastasis was identified by PET/CT. Endorectal MR imaging, however, was locally positive in 15 of 18 patients. Of the 19 patients who were evaluable 6 months after salvage radiotherapy, 12 responded with a marked decrease in PSA level (half or more from baseline). The authors concluded that although the 2 PET/CT techniques succeeded in detecting local residual or recurrent disease in about half of patients with PSA levels <1 ng/mL after radical prostatectomy, "these studies cannot yet be recommended as a standard diagnostic tool for early relapse or suspicion of subclinical minimally persistent disease after surgery." They noted that endorectal MR imaging might be more helpful, especially in patients with a low likelihood of distant metastases. They added that "further research with ^{18}F-choline or ^{11}C-acetate PET/CT with optimal spatial resolution might be needed for patients with a high risk of distant relapse after radical prostatectomy even at low PSA values."

BJU International

THERAPY

Immunoscintigraphy Targeting in Head and Neck Cancer

Birchler et al. from University Hospital Zurich (Switzerland) reported in the April issue of *Otolaryngology—Head and Neck Surgery* (2007;136:543–548) on the results of a phase I/II clinical study investigating tumor targeting in patients with head and neck squamous cell carcinomas, using SPECT/CT and PET/CT to detect tumor targeting by an antibody directed against the extra-domain-B (EDB) of fibronectin, a marker of angiogenesis and tissue remodeling. The study included 5 patients who were injected with the ^{123}I-L19(scFv)2 antibody and underwent both SPECT/CT and PET/CT. Successful targeting of the primary tumor was visualized on SPECT/CT in 4 of the 5 patients, and these images were comparable to PET imaging. The authors concluded that not only is tumor targeting with SPECT/CT and this antibody feasible for head and neck squamous cell carcinoma, but that "these results may serve as a base for future therapeutical applications in human beings, with modified versions of the L19(scFv)2 antibody designed to selectively deliver bioactive molecules into malignant tumors."

Otolaryngology—Head and Neck Surgery

Anti-α_v Integrin mAb Therapy in Advanced Solid Tumors

In an article published in the April 1 issue of *Clinical Cancer Research* (2007;13:2128–2135), Mullamitha et al. from Cancer Research UK and Christie Hospital (Withington, UK) reported on a phase I study of the safety and pharmacokinetics of a fully human monoclonal antibody to anti-α_v integrins (CNTO 95) that has been shown in preclinical studies to inhibit angiogenesis and tumor growth. The study included 24 patients with advanced refractory solid tumors who were infused with the antibody on days 0, 28, 35, and 42 and who underwent clinical assessment, dynamic contrast-enhanced MR imaging, and ^{18}F-FDG PET imaging. The infusions were generally well tolerated, although 5 patients experienced infusion-related fevers that responded to acetaminophen. Six patients who

achieved stable disease or improvement were eligible for extended dosing every 3 weeks for a period of up to 1 year. Pre- and posttreatment lesion biopsies confirmed tumor cell α_v integrin expression, CNTO 95 penetration of tumors, and localization to tumor cells in association with reduced bcl-2 expression. In 1 patient with stable ovarian carcinosarcoma, the original lesion was no longer visualized on PET at day 49. The authors concluded that the confirmation of tumor localization and pharmacodynamic activity, in combination with the relative absence of adverse effects, indicates promise for this approach in the treatment of solid tumors.

Clinical Cancer Research

^{18}F-FMISO PET and Reoxygenation Dynamics

In an article e-published on March 28 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics,* Thorwarth et al. from University Hospital Tubingen (Germany) reported on a study designed to use serial^{18}F-fluoromisonidazole (^{18}F-FMISO) PET imaging to develop a model for reoxygenation dynamics and to elucidate their relationship to local control after radiotherapy (RT) for head and neck cancer. The study included 10 patients with head and neck cancer who underwent ^{18}F-FMISO PET imaging before RT with 70 Gy and after approximately 20 Gy. Patients also underwent CT at 8–24 months after completion of RT to assess for local recurrence. The authors devised a probability model based on tumor-specific values for the level of tracer retention and vascular perfusion efficiency that yielded estimates of time to reoxygenation. Using this model, a malignancy value (M) was calibrated by a fit to the observed outcome data, so that reoxygenation was reflected as a progression to less-malignant tumor types (i.e., smaller values of M). In the pretreatment scans, 4 patients showed no hypoxia and 6 patients showed severe hypoxia. In 4 of the 6 hypoxic patients, M decreased after 20 Gy, but the remaining 2 showed increases in M values. The authors concluded that this tumor control probability model, which combines local perfusion efficiency and degree of hypoxia to estimate reoxygenation time, constitutes "a key for hypoxia image-guided dose escalation in RT."

International Journal of Radiation Oncology, Biology, Physics

MOLECULAR IMAGING

Triple-Fusion Reporter Gene Vectors for Multimodality Imaging

Ray et al. from Stanford University (CA) and the University of California–San Diego reported in the April 1 issue of *Cancer Research* (2007;67:3085–3093) on the construction and validation of improved triple-fusion reporter gene vectors for multimodality molecular imaging of living animals. The combination of a bioluminescent, fluorescent, and PET reporter genes was validated in cell culture and in a mouse model. The authors described initial studies and improvements to the triple-fusion reporter vector and noted that it will "enable high sensitivity detection of lower numbers of cells from living animals using bioluminescence, fluorescence, and microPET imaging techniques" in investigations on the location, magnitude, and time variation of reporter gene expression in small animals.

Cancer Research

Optical Visualization of Cathepsin K Activity

In an article e-published on April 9 ahead of print in *Circulation*, Jaffer et al. from the Massachusetts General Hospital and Harvard Medical School (Boston, MA) reported on the development and initial studies of a novel near-infrared fluorescence sensor probe for optical imaging of cathepsin K activity in mouse and human atherosclerosis. Cathepsin K is a potent elastinolytic and collagenolytic cysteine protease that is believed to participate in the evolution and destabilization of atherosclerotic plaques. The authors described the development and activity of the probe and the results of optical imaging of atheroma in vivo in apolipoprotein E (–/–) mice and ex vivo in human carotid endarterectomy specimens. In both in vivo and ex vivo studies, the probe identified localization of enzymatically active cathepsin K in the vicinity of cathepsin K–positive macrophages and in disrupted elastin fibers within the media underlying plaques. They concluded that results with this promising probe indicate that "augmented cathepsin proteolysis in atheromata further links cathepsin K to vascular remodeling and plaque vulnerability."

Circulation

Targeted Optical Imaging of Colonic Tumors

Deane et al. from Vanderbilt University (Nashville, TN) reported in the April issue of *Molecular Cancer Research* (2007;5:341–349) on the development of a high-throughput in vivo imaging approach to detect spontaneously arising colonic tumors in mice using a novel peripheral benzodiazepine receptor (PBR)–targeted molecular imaging agent. NIR-conPK11195 is a transmitochondrial membrane protein that modulates steroid biosynthesis. In experiments with Smad3 (–/–) mice, the tracer localized in colonic adenomas and carcinomas, which were detected with a sensitivity of 67% and specificity of 86% 13 hours after injection. Moreover, the tracer was not retained in nonneoplastic hamartomas or chronically inflamed colonic tissue. The authors concluded that these results indicate that "NIR-conPK11195 is a promising optical molecular imaging tool to rapidly screen for colonic tumors in mice and to discriminate inflammation from cancer."

Molecular Cancer Research

Reporter Gene Imaging in Prostate Cancer Gene Therapy

Siddiqui et al. from the Henry Ford Health System (Detroit, MI) reported

on April 4 ahead of print in *Human Gene Therapy* on a study describing design considerations for incorporating sodium iodide symporter (NIS) reporter gene imaging into phase I prostate cancer gene therapy trials. The studies were conducted in a canine model of soft tissue sarcoma and were designed to determine the dosimetric characteristics of the authors' reporter gene system coupled with intravenous administration of ^{99m}Tc-labeled sodium pertechnetate and to assess the feasibility of using human NIS (hNIS) as a reporter gene for SPECT imaging of the dynamics of adenoviral transgene expression in a large animal tumor. Uptake in tumors in all animals was detected by SPECT and remained visible on imaging up to 4 days. Using highest values in studies from 25 dogs, the absorbed radiation dose to critical organs was calculated and found to be below U.S. Food and Drug Administration limits for diagnostic imaging. The authors concluded that on the basis of these dosimetry calculations, "up to 5 imaging procedures can be safely performed in humans after intraprostatic injection of the Ad5-yCD/mutTK(SR39)rep-hNIS adenovirus" and that the "hNIS reporter gene system can be used to study the dynamics of adenoviral gene therapy vectors in large animal tumors."

Human Gene Therapy

SPECT Imaging of Viral Biodistribution

In an article e-published on April 5 ahead of print in *Gene Therapy*, Raty et al. from the AI Virtanen Institute for Molecular Sciences and Ark Therapeutics (Kuopio, Finland) reported on microSPECT imaging of the biodistribution of a ^{99m}Tc-DTPA-biotin–labeled avidin-displaying baculovirus in a rat model. Virus injection was through 4 different routes, and imaging results suggested that although the virus spread via the lymphatic network after all routes, that localization and accumulation varied by administrative route. Specific results led the authors to conclude that "the baculovirus may be beneficial for the treatment of kidney diseases" via the intraperitoneal route. The study is 1 example of the ways in which molecular imaging of viruses is providing essential information about biodistribution for the development of targeted gene therapy vectors.

Gene Therapy

Intracoronary Autologous Bone Marrow Cell Therapy

Qiam et al. from the Peking Union Medical College and Chinese Academy of Medical Sciences (Beijing, China) reported on April 3 ahead of print in the *Journal of Cell Biochemistry* on a SPECT study of tissue distribution in intracoronary delivery of ^{18}F-FDG-labeled autologous bone marrow mononuclear cells in a postinfarct swine model. One week after induction of acute myocardial infarction in the swine, the radiolabeled bone marrow cells were administered using a coronary catheter into the infarct-affected coronary artery. SPECT images were acquired 1 hour after cell infusion. Injected cell activity (6.8%) was detected in the infarcted myocardium, with the remaining activity mainly in liver and spleen. Within the heart, bone marrow mononuclear cells were detected predominantly in underperfused myocardium. Six weeks after infusion, swine were killed and pathology indicated that swine hearts that had received the cell infusions showed less fibrosis and inflammatory infiltrate, more viable tissue, and higher vascular density, than hearts from postinfarction swine that did not receive the infusion. Cardiac function was significantly improved in the mononuclear cell infused–hearts. The authors concluded that "^{18}F-FDG labeling and dual-nuclide SPECT imaging is capable of monitoring in vivo distribution and homing of bone marrow mononuclear cells after intracoronary infusion" and that such infusion "may improve cardiac function and positive ventricular remodeling in the heart with acute myocardial infarction."

Journal of Cell Biochemistry

Optical Probe Imaging and Peritoneal Micrometastases

In an article in the April 15 issue of *Cancer Research* (2007;67:3809–3817), Hama et al. from the National Cancer Institute (Bethesda, MD) reported on a 2-step activation process for pretargeted fluorescent molecular imaging of peritoneal metastases. In this approach, tumors were pretargeted with a nonfluorescent biotinylated monoclonal antibody, followed by a fluorescent conjugate that binded to the previously targeted antibody. The result was an almost 10-fold amplification of the optical fluorescence signal and high tumor-to-background ratios. In vivo studies were conducted with spectral fluorescence imaging in a mouse model of peritoneal metastasis using a HER1-overexpressing cell line after pretargeting with biotinylated cetuximab and 3 hours after administration of the fluorescent conjugate. Both aggregated tumors and small cancer implants were easily visualized, with a sensitivity of 96% and specificity of 98% for lesions $\geq$0.8 mm. The authors concluded that this 2-step activation paradigm "could be useful in tumor-specific molecular imaging of various targets to guide surgical resections."

Cancer Research