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 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.

DIAGNOSIS

Dopamine and Conditioned Responses in Addiction

Volkow et al. from the National Institute on Drug Abuse (Bethesda, MD), the National Institute on Alcohol Abuse and Alcoholism (Bethesda, MD), and the Brookhaven National Laboratory (Upton, NY) added to their growing body of nuclear medicine studies on the effects of addiction in the human brain with an article published on July 14 in the *Journal of Neuroscience* (2006;26:6583–6588). The group used ^{11}C-raclopride PET to investigate cocaine craving by assessing dopamine changes in the dorsal striatum in response to "conditioned stimuli." The study included 18 cocaine-addicted individuals who were imaged with PET immediately after watching a neutral video (nature scenes) and again immediately after watching scenes of subjects smoking cocaine. Tracer binding in dorsal but not in ventral striatum was significantly reduced after the cocaine-cue video, and the magnitude of this reduction correlated with self-reports of craving. Individuals with the highest scores on measures of withdrawal symptoms and of addiction severity had the largest dopamine changes in dorsal striatum. The authors concluded that, "This provides evidence that dopamine in the dorsal striatum (region implicated in habit learning and in action initiation) is involved with craving and is a fundamental component of addiction." They noted that strategies aimed at inhibiting dopamine increases from conditioned responses should be beneficial in therapeutic approaches to cocaine addiction.

Journal of Neuroscience

PET and CNS Myelin

Stankoff et al. from the Institut National de la Sante et de la Recherche Medicale (Paris, France) reported in the June 13 issue of the *Proceedings of the National Academy of Sciences USA* (206;103:9304–9309) on a proof-of-concept study using PET to image central nervous system (CNS) myelin. They described 1,4-bis(p-aminostyryl)-2-methoxy benzene (BMB), a synthesized fluorescent molecule that binds selectively to myelin both ex vivo and in vivo and detailed initial studies in which ^{11}C-BMB PET was used for in vivo brain myelin imaging in a baboon. In other preliminary in vivo and ex vivo studies, the tracer was found to cross the blood–brain barrier after systemic injection and to bind to myelin in a dose-dependent and reversible manner. In ex vivo multiple sclerosis brain samples, for example, different levels of BMB binding differentiated remyelination in shadow plaques from either demyelinated lesions or normal-appearing white matter. The technique holds special promise as new therapies are developed for demyelinating disorders. Reliable approaches for assessing and quantifying remyelination will be essential in clinical trials and in the continued development of beneficial treatments.

Proceedings of the National Academy of Sciences USA

Aging and BBB P-Glycoprotein Function

In the June issue of *Clinical Pharmacology and Therapeutics* (2006; 79:540-548), Toornvliet et al. from the VU University Medical Centre (Amsterdam, The Netherlands) reported on the use of ^{11}C-verapamil PET to assess the effect of increasing age on functional P-glycoprotein in the blood–brain barrier. The study included 5 healthy young volunteers (ages, 21–27 years) and 5 healthy older volunteers (ages, 59–68 years). All underwent ^{11}C-verapamil PET imaging to assess gray matter P-glycoprotein function. The mean volume of distribution value for the younger group was 0.62 ± 0.10 and for the older group was 0.73 ± 0.07. The index of P-glycoprotein activity in CD3-positive leukocytes was 2.88 ± 0.77 in the younger group and 1.76 ± 0.58 in the older group. Loss of P-glycoprotein function has been associated with the development and progression of neurodegenerative diseases. Moreover, P-glycoprotein is an efflux transporter responsible for the passage of various drugs across the blood–brain barrier. The authors concluded from their findings that P-glycoprotein activity is decreased during aging and that with this decrease the brain may be exposed to higher drug and toxin levels.

Clinical Pharmacology and Therapeutics

^{11}C-MET PET/CT/MR and Treatment Planning

In an article e-published ahead of print on June 7 in the *International Journal of Radiation Oncology, Biology, Physics*, Grosu et al. from the

Technical University of Munich (Germany) and the University of California at Los Angeles reported on the role of ^{11}C-methionine (^{11}C-MET) PET in target volume delineation for meningiomas to be treated with stereotactic fractionated radiotherapy. The study included 2 readers who performed treatment planning in each of 10 patients scheduled for radiotherapy. In the first step, they planned on the basis of information from coregistered CT and MR images. In the second step, ^{11}C-MET PET information was added to the coregistered CT/MR images. They found that the correlation between the gross tumor volumes assessed by the 2 observers was 0.855 with the CT/MR images and 0.988 when the PET data were added. The number of patients with agreement in >80% of the outlined volume increased with the availability of PET from 1 in 10 to 5 in 10. The median volume of intersection between the regions delineated by the observers increased from 69% to 79% with PET. The authors concluded that their results "provide arguments for invasive studies of the correlation between MET-PET images and histologic tumor extension and for prospective trials of target volume delineation with CT/MRI/MET-PET image fusion."

International Journal of Radiation Oncology, Biology, Physics

PET and Donepezil in AD

Teipel et al. from the Ludwig-Maximilian University (Munich, Germany) reported in the July issue of *Psychopharmacology* (Berlin; 2006; 187:86–94) on a study designed to use ^{18}F-FDG PET to determine the effects of treatment with donepezil, a centrally selective acetylcholinesterase inhibitor, on cortical metabolism in patients with Alzheimer's disease (AD). The study included 23 patients with mild-to-moderate probable AD (18 of whom completed the study), who participated in a double-blind crossover trial of 8 weeks donepezil and 8 weeks placebo, with repeated ^{18}F-FDG PET examinations during passive audiovisual stimulation. The authors found that cognitive measures did not differ after donepezil treatment and after placebo. During passive audio-visual stimulation, all patients showed activation in posterior visual and auditory areas and decreased activation in frontal cortex and basal ganglia. However, with donepezil, resting state metabolism was increased in left prefrontal cortex and decreased in right hippocampus, and cortical response to activation was increased in right hippocampus. The authors concluded that donepezil treatment "shows a spatially limited functional effect on right hippocampus and left prefrontal cortical metabolism, independently of clinical response to treatment."

Psychopharmacology

Predicting PET Tracer Binding Potential

In an article e-published on June 21 ahead of print in the *Journal of Cerebral Blood Flow and Metabolism*, Morris and Yoder from Indiana University (Indianapolis) proposed a mathematical method for predicting the utility of any PET tracer as a detector of changes in the concentration of an endogenous competitor via displacement of the tracer. Such a model would provide assessments of tracers that might provide noninvasive assays of fluctuations in synaptic neurotransmitter levels. The authors described PET Displacement Sensitivity (PDS), a tracer-specific predictor that is calculated from compartmental model simulations of the uptake and retention of dopaminergic radiotracers in the presence of transient elevations of dopamine. PDS predicts the change in binding potential for a specific change in receptor occupancy because of binding by the endogenous competitor. They reported on simulations with the PDS yielding the following results: for D_2/D_3 tracers, the calculated PDS indices suggested a rank order (highest to lowest) for sensitivity to displacement by dopamine to be: raclopride, fallypride, fluoroethylspiperone, FLB, *N*-methylspiperone, and epidepride.

Journal of Cerebral Blood Flow and Metabolism

Review: ^{18}F-FDG PET in RT Planning

van Baardwijk et al. from the University of Maastricht (The Netherlands) presented a critical review of the current status of ^{18}F-FDG PET in tumor volume delineation in radiation therapy treatment planning in the June issue of *Cancer Treatment Reviews* (2006;32:245–260). In a wide-ranging review of the literature, the research team asked whether the use of PET in tumor definition improves outcomes in radiotherapy and whether such improvement is likely to be from reduced toxicity and/or higher tumor control probability. They noted the incremental value provided by the anatomic component of CT in PET/CT imaging, with which interobserver variability seemed to be reduced. They concluded that although the use of PET is seen to provide measurable improvements in tumor delineation, lymph node identification, and sparing of healthy tissue in lung and esophageal cancers and lymphoma, "not enough data are currently available to draw definitive conclusions about the role of PET in radiation treatment planning" in other cancers and tumor sites.

Cancer Treatment Reviews

PET/CT and Other Modalities in Myeloma

In an article e-published ahead of print on June 7 in *Skeletal Radiology*, Breyer et al. from the University of Maryland Medical Center (Baltimore, MD) compared ^{18}F-FDG PET/CT with conventional imaging modalities in the management and staging of myeloma. The study included PET/CT scans and all other available imaging data from 16 consecutive patients with multiple myeloma. The patients had undergone a total of 79 imaging procedures: 16 PET/CT scans, 16 radiographs (including 13 skeletal surveys), 25 CT

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scans (16 chest, 3 abdominal, 4 pelvic, 1 spine, 1 neck), and 22 MR imaging studies (17 spine, 3 pelvic, 2 extremity). Areas of abnormal uptake on PET were correlated with the other imaging studies. PET/CT scans were reviewed to see whether small lesions identified on the other imaging studies might be seen in retrospect. PET/CT scans revealed a total of 104 sites (90 in bone, 14 soft tissue) of abnormal uptake. Fifty-seven of these sites (55%) were new or previously undetected. The other imaging modalities combined with clinical information confirmed the other 47 areas but also revealed 133 additional small skeletal lesions. Only 6 of these 133 lesions showed mild tracer uptake on review of the PET/CT images. PET/CT findings led to management changes in 9 of the 16 patients, but MR also indicated 5 instances of diffuse bone involvement not evident on PET/CT. The authors concluded that although PET/CT is useful for the management and staging of myeloma, it should be combined with other modalities. They noted that, "if PET/CT were the sole imaging study done, it would miss many additional small lytic skeletal lesions and could miss diffuse spine involvement."

Skeletal Radiology

^{18}F-FDG Uptake and Subtypes of Hodgkin's Lymphoma

Hutchings et al. from Copenhagen University Hospital (Denmark) reported on May 16 ahead of print in *Hematological Oncology* on a study investigating variations in standardized uptake values (SUVs) in ^{18}F-FDG PET evaluation of different histopathologic subtypes of Hodgkin's lymphoma. The study included 60 patients with newly diagnosed Hodgkin's lymphoma who underwent PET/CT for staging after lymph node biopsy. Maximum SUVs in each patient and in each affected region or organ were recorded. Identified disease subtypes included 7 patients with nodular lymphocytic predominance (NLP; average total maximum SUV = 9.3 g/mL), 38 patients with nodular sclerosis (NS; average total maximum SUV = 16.3 g/mL), 11 patients with mixed cellularity (MC; average total maximum SUV = 20.8 g/mL), and 4 patients with unclassified classical HL (CHL; average total maximum SUV = 19.5 g/mL). Out of a total of 780 sites in all patients (600 lymph node regions plus 180 organs), 208 were affected with Hodgkin's lymphoma. Mean maximum SUVs in these sites by subtype were: 12 sites with NLP, 8.3 g/mL; 147 sites with NS, 11.2 g/mL; 36 sites with MC, 14.6 g/mL; and 13 sites with CHL, 13.1 g/mL. The authors concluded that "there is a significant difference in FDG/glucose uptake between the different histopathological subtypes" of Hodgkin's lymphoma.

Hematological Oncology

PET and Stem Cells in Lymphoma

In an article e-published ahead of print on June 12 in *Bone Marrow Transplantation*, Svoboda et al. from the Abramson Cancer Center of the University of Pennsylvania (Philadelphia) reported on the prognostic value of ^{18}F-FDG PET in lymphoma patients scheduled to undergo autologous stem cell transplantation. The retrospective study included 50 patients with lymphoma (Hodgkin's disease and non-Hodgkin's lymphoma) who underwent ^{18}F-FDG PET imaging after at least 2 cycles of salvage chemotherapy and before autologous stem cell transplantation. Results of imaging placed patients into ^{18}F-FDG PET–negative (32 patients) or –positive (18 patients) groups. In the uptake-negative group, median progression-free survival was 19 months (range, 2–59 months) with 15 (54%) patients without progression at 12 months after transplantation. Median overall survival for this group was not reached during the study follow-up period. Median progression-free survival was 5 months (range, 1–19 months) in the uptake-positive group, with only 1 patient without progression at 12 months after transplantation and a median overall survival of 19 months (range, 1–34 months). In the uptake-negative group, chemotherapy-resistant patients by CT-based criteria had comparable outcomes to those with chemotherapy-sensitive disease. The authors concluded that "a positive FDG PET scan after salvage chemotherapy and prior autologous stem cell transplantation indicates an extremely poor chance of durable response" after transplantation.

Bone Marrow Transplantation

Significance of Lobar Location in NSCLC

Cerfolio and Bryant from the University of Alabama (Birmingham) reported in the June issue of the *Annals of Thoracic Surgery* (2006; 81:1969–1973) on a retrospective study designed to evaluate the distribution and likelihood of lymph node metastasis based on the lobar location of the primary tumor in non–small cell lung cancer (NSCLC). The authors conducted a retrospective review of incidence and location of N2 disease in 954 patients with NSCLC who underwent PET/CT for staging followed by nodal biopsy and/or resection with complete lymphadenectomy. They found that the percentages of N2 disease by location were: right upper lobe, 27% (most often in the 4R, 23%); right middle lobe, 15% (most often in the 4R, 8%, and 7th station, 6%); right lower lobe, 30% (most often in the 4R, 15%, and 7th station, 14%); left upper lobe, 20% (most often in the 6th station, 16%); and left lower lobe, 22% (most often in the 7th station, 8%). Patients with right-sided cancers were more likely to have N2 disease than those with left-sided lesions (27% and 21%, respectively). The authors concluded that they had identified a "distinct predilection for the location of N2 disease based on the lobar location of primary NSCLC" and recommended consideration of video-assisted thoracoscopy for biopsy of the

5th and 6th stations for patients with left upper lobe lesions, mediastinoscopy for right upper lobe lesions, and esophageal ultrasound with fine-needle aspiration for right lower lobe, left lower lobe, and right middle lobe lesions.

Annals of Thoracic Surgery

MR and PET in Breast Cancer

Semple et al. from the University of Aberdeen (United Kingdom) reported on June 20 ahead of print in the *Annals of Oncology* on a study investigating whether pretherapy vascular delivery assessment with contrast-enhanced MR imaging can predict reduction in breast cancer metabolism as assessed by ^{18}F-FDG PET after a single cycle of chemotherapy. The study included 17 patients with large or locally advanced invasive ductal carcinomas of the breast who were imaged with contrast-enhanced MR and PET before chemotherapy and 20 days after the first cycle of chemotherapy. A significant association was observed between pretherapy MR vascular parameters and the reduction in PET metabolism after 1 cycle of chemotherapy. The authors concluded that this suggests that "reduction in PET metabolism as a result of chemotherapy may be dependent, at least in part, on pretherapy vascular delivery," the characteristics of which may be suitable for use as a surrogate measure for initial chemotherapy delivery.

Annals of Oncology

THERAPY

^{131}I Therapy and Ob/Gyn Abnormalities

In an article e-published on June 15 ahead of print in *Fertility and Sterility*, Sioka et al. from the Army Share Fund Hospital (Athens, Greece) reported on abnormalities in the menstrual cycle and/or pregnancy in women after ^{131}I therapy for thyroid cancer. The study included 45 ^{131}I-treated women under 40 years of age as well as 83 age-matched women as controls. Data were derived from a review of charts and from telephone interviews. Fourteen of 45 women (31.1%) reported menstrual cycle irregularities after radioiodine treatment. Twelve women (14.5%) in the control group reported menstrual cycle irregularities. Menstrual cycle and menses irregularities in the treatment group seemed to increase with age. Six previously treated women (13.3%) delivered a total of 7 children, with no premature births or miscarriages reported. The authors concluded that despite significant increases in menstrual cycle and/or menses irregularities after treatment with ^{131}I, radioiodine therapy did not result in subsequent pregnancy abnormalities.

Fertility and Sterility

External-Beam RT After RIT

Justice et al. from the Mayo Clinic (Rochester, MI) reported on June 12 ahead of print in *Cancer* on a study designed to evaluate the safety and efficacy of external-beam radiation therapy (RT) for non-Hodgkin's lymphoma (NHL) in patients who had previously undergone ^{90}Y-ibritumomab tiuxetan radioimmunotherapy (RIT). The retrospective study included 19 patients with relapsed B-cell NHL who had received RIT with ^{90}Y-ibritumomab tiuxetan and who subsequently received external-beam RT to a total of 39 tumor sites. Complete RT records were available for only 16 of these patients (36 tumor sites), and response data were available for 29 treated sites. The overall response rate was 90% (26/29), with 12 complete responses (41%), 7 complete clinical responses (24%), 7 partial responses (24%), and 3 reported as stable (10%). Toxicities were reported as transient and reversible and corresponded to the anatomic regions treated by RT. The authors concluded that external-beam RT can produce tumor responses at sites of NHL that relapse after RIT and can do so with acceptable toxicity.

Cancer

RIT in Hepatocellular Carcinoma

In an article published in the June 1 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2006;65:435–444), Chen et al. from the Fourth Military Medical University (Xi'an, China) reported on clinical phase I/II trials of a novel ^{131}I-labeled monoclonal antibody–based radioimmunotherapy (RIT) targeted at the treatment of patients with hepatocellular carcinoma. The phase I trial included 28 patients who received hepatic artery infusions of varying amounts of the RIT agent. In the multicenter phase II trial, 106 patients received 27.75 MBq/kg on day 1 of a 28-day cycle, which was determined to be a safe dosage, with no life-threatening toxic effects noted. Of the 73 patients completing 2 cycles of treatment, 6 (8.22%) experienced a partial response, 14 (19.18%) a minor response, and 43 (58.90%) had stable disease. The 21-month survival rate was 44.54% among those treated. The authors concluded that this RIT regimen is "safe and active" for patients with hepatocellular carcinoma.

International Journal of Radiation Oncology, Biology, Physics