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, and these shifting lines are reflected in the briefs presented here. This month, the most recent literature contained an unusually rich and diverse spectrum of articles on new applications in brain and head imaging.

DIAGNOSIS

Methylphenidate and Brain Glucose Metabolism

Volkow and colleagues from the National Institute on Drug Abuse (Bethesda, MD) and the Brookhaven National Laboratory (Upton, NY) reported on April 16 in the online journal *PloS ONE* on a study indicating that an agent currently in widespread elective use as a cognitive enhancer exerts its action by decreasing the amount of glucose needed by the brain to perform cognitive tasks. In addition to applications in attention-deficit hyperactivity disorder, methylphenidate and amphetamine use has been reported among students and others (including physicians) to enhance concentration span, memory skills, and attention focus. However, the mechanism by which these agents work in the brain is unclear, as is the reason why some individuals respond to these stimulants, others do not, and still others register a depressive rather than stimulative response. Volkow and colleagues have previously reported on numerous innovative studies investigating the relationship between stimulant action and dopamine receptors in the brain as assessed by PET. The current study included 23 healthy adult volunteers who underwent PET imaging at baseline and while performing a series of numerical calculations, once with and once without methylphenidate administration. Results from a fourth scan were available from 16 participants who were administered methylphenidate without performing the cognitive task. Methylphenidate was found to significantly reduce (by 50%) the amount of glucose utilized by the brain when performing the cognitive task, an effect not seen in individuals at baseline. Although this reduction in metabolic increases could be seen in whole-brain glucose metabolism, reductions in regions associated with "mind wandering" (default network) occurred only in individuals in whom these areas were stimulated when performing the cognitive tasks without methylphenidate. The authors noted that "these results corroborate prior findings that stimulant medications reduced the magnitude of regional activation to a task and in addition document a 'focusing' of the activation," an effect that could be beneficial when neuronal sources are diverted or impaired but could be detrimental when the brain is already fully focused. They suggested this as an explanation for the varying responses to methylphenidate administration.

PloS ONE

^{18}F-Fallypride PET in Schizophrenia

In an article e-published on April 16 ahead of print in *Neuropsychopharmacology*, Kegeles et al. from the Columbia University College of Physicians and Surgeons (New York, NY) reported on a dose-occupancy study using ^{18}F-fallypride PET to assess D_2 receptor occupancy of an approved atypical antipsychotic medication in patients under treatment for schizophrenia or schizoaffective disorder. The study included 19 such patients being treated with varying levels of aripiprazole, each of whom underwent ^{18}F-fallypride PET to assess mean regional occupancies and a model-independent estimate of the medication's effect on pituitary binding, as well as Positive and Negative Syndrome Scale (PANSS) scoring. Occupancy levels were found to be high across regions of interest (higher in extrastriatal than striatal areas) and varied directly with dosage. Positive (but not negative) symptom improvements as assessed by PANSS correlated with striatal but not extrastriatal occupancies. The authors concluded that "Correlations of ratings of clinical improvement with regional occupancy suggest that aripiprazole, as do other antipsychotics, benefits positive symptoms of schizophrenia most directly through its modulation of striatal rather than cortical or other extrastriatal dopamine activity."

Neuropsychopharmacology

PET and Responses to Levodopa

In the April 16 issue of the *Journal of Neuroscience* (2008;28:4201-4209), Hirano et al. from the Feinstein Institute for Medical Research (Manhasset, NY) reported on a study using ^{15}O-H_2O and ^{18}F-FDG PET to compare the metabolic and neurovascular effects of levodopa therapy for Parkinson's disease (PD). The study included 11 patients with PD who were scanned with both tracers in the unmedicated state and during intravenous infusion of levodopa. The resulting images were assessed for changes in motor- and cognition-related covariance patterns in cerebral blood flow and cerebral metabolic rate for glucose. These changes in network activity were then compared with those occurring during

subthalamic nucleus deep brain stimulation and those observed in a test–retest control group of patients with PD. The authors identified a significant dissociation between cerebral blood flow and cerebral glucose metabolic rate in levodopa modulation of the PD motor-related network. Network activity was reduced in the metabolic scans at the same time that activity was increased in the cerebral blood flow scans. This dissociation between flow and metabolism was also seen at the regional level, with levodopa-mediated reductions in cerebral glucose metabolic rate and increases in cerebral blood flow in the putamen/globus pallidus, dorsal midbrain/pons, subthalamic nucleus, and ventral thalamus. Cerebral blood flow responses to levodopa in the putamen and pons were greater in patients with drug-induced dyskinesia. These flow–metabolism dissociations were not present in the group imaged during subthalamic deep stimulation or in the control group of patients with PD. The authors concluded that these findings suggest that "flow–metabolism dissociation is a distinctive feature of levodopa treatment" and that this phenomenon may be especially pronounced in patients with levodopa-induced dyskinesia.

Journal of Neuroscience

^{11}C-PiB PET in APP Locus Duplication

Remes et al. from the University of Oulu (Finland) reported in the April issue of the *Archives of Neurology* (2008;65:540–544) on a study using ^{11}C-labeled Pittsburgh Compound B (^{11}C-PiB) PET and MR imaging to investigate amyloid accumulation in patients with hereditary cerebral amyloid angiopathy and amyloid precursor protein (APP) locus duplication. The study focused on 2 siblings (ages, 49 and 60 y) with APP locus duplication and diagnoses of hereditary Alzheimer's disease and cerebral amyloid angiopathy. Uptake results on PET imaging were compared with results from controls. Tracer uptake was found to be increased in the striatum (caudate nucleus, 225% and 280% of the control mean; putamen, 166% and 185% of the control mean) and the posterior cingulate (to 168% and 198% of the control mean) and marginally increased in other cortical brain areas. The authors noted that the pattern of increased uptake was different from that seen in patients with typical (non-APP locus duplication–associated) Alzheimer's disease. They concluded that "Amyloid imaging with ^{11}C-PiB PET is a useful tool for detecting in vivo amyloid accumulation in patients with hereditary cerebral amyloid angiopathy."

Archives of Neurology

DBS and Symptom Improvement in PD

In a study e-published on April 15 ahead of print in *Movement Disorders*, Strafella et al. from the University of Toronto (Canada) reported on a ^{15}O-H_2O PET study measuring changes in regional cerebral blood flow (rCBF) in a patient with advanced Parkinson's disease at rest and during off/on deep brain stimulation of the pedunculopontine nucleus (PNN). The patient underwent imaging at rest and during unilateral PNN deep brain stimulation. Stimulation was found to bilaterally increase rCBF in subcortical areas, especially the thalamus. Clinical evaluation showed an approximately 20% subsequent improvement in motor function. The use of PET in this study provided novel evidence that deep brain stimulation of the human brain may be able to modify rCBF in closely connected subcortical structures. The authors concluded that "Given the importance of the PPN in locomotion, control of posture, and behavioral states, deep brain stimulation may have significant implications for more complicated forms of movement disorders where deterioration of gait, postural instability, and rapid-eye movement sleep behavior disorders are very disabling."

Movement Disorders

PET and Brain Receptor Occupancy for Antihistamine

In an article e-published on April 11 ahead of print in the *British Journal of Pharmacology*, Tashiro et al. from Tohoku University (Sendai, Japan) reported on the use of ^{11}C-doxepin PET imaging to measure histamine H_1 receptor occupancy for beptastine besilate, a novel second-generation oral antihistamine with demonstrated antiallergic effects but without adequate assessment of sedative properties. The study included 8 healthy male volunteers who underwent ^{11}C-doxepin PET scanning after a single oral administration of bepostatine, diphenhydramine, or placebo in a crossover study design. Binding potential ratios and H_1 receptor occupancy levels were calculated from the placebo data and compared with bepotastine and diphenhydramine results in various brain regions. The authors found that mean histamine H_1 receptor occupancy percentages were significantly lower after bepostatine administration than after diphenhydramine in all cortical areas (14.7% and 56.4%, respectively). They concluded that "Oral bepotastine (10 mg), with its relatively low histamine H_1 receptor occupancy and thus minimal sedation, has the potential for use as a mildly or slightly sedative antihistamine in the treatment of various allergic disorders." The study provides another example of ways in which molecular imaging is delivering valuable information for drug development, approval, and patient benefit.

British Journal of Pharmacology

Exploring Lithium's Neuroprotective Effects

Omata et al. from the University of Fukui (Japan) reported in the May issue of *Bipolar Disorders* (2008;10: 360–368) on an in vitro study using dynamic positron autoradiography with ^{18}F-FDG to elucidate the neuroprotective effect of chronically or acutely administered lithium against hypoxia in several brain regions. The study was conducted in brain slices prepared from rats that had been administered lithium either chronically or acutely and from control rats. Autoradiography was used to measure cerebral glucose metabolic rate (CMRglc) before and after hypoxia loading to brain slices. Western blot analysis assessed lithium-

induced changes in expression of proteins. After hypoxia loading, the CMRglc of the chronic lithium treatment group recovered in the frontal cortex, caudate putamen, hippocampus, and cerebellum but not in the thalamus. The CMRglc did not recover in any analyzed brain regions in the acute lithium treatment group. After chronic lithium treatment, levels of expression of brain-derived neurotrophic factor and phospho-cAMP response element binding protein were higher than those of untreated rats in the frontal cortex but not in the thalamus. The authors concluded that "These results demonstrated that lithium was neuroprotective against hypoxia only after chronic treatment and only in specific brain regions, and that cAMP response element binding protein and brain-derived neurotrophic factor might contribute to this effect."

Bipolar Disorders

^{18}F-FLT PET in Glioma Proliferation

Ullrich et al. from the Max Planck Institute for Neurological Research and the Klaus-Joachim Zülch Laboratories (Cologne, Germany) reported in the April 1 issue of *Clinical Cancer Research* (2008;14:2049–2055) on a study designed to investigate the relationship between in vivo derived kinetic parameters for ^{18}F-fluorothymidine (^{18}F-FLT) and the proliferation rate measured in vitro by Ki-67 staining in patients with newly diagnosed high-grade gliomas. The study included 13 such patients who underwent ^{18}F-FLT PET, ^{11}C-methionine (^{11}C-MET) PET, and T1-, T2-, and gadolinium T1-weighted MR imaging on consecutive days. Tracer kinetic parameters, standardized uptake values, and tumor-to-background ratios were determined for the radiotracers and contrasted with results from Ki-67 assessment. The researchers identified a significant correlation between the metabolic rate constant Ki and the proliferation index measured by Ki-67 immunostaining. In addition, the phosphorylation rate constant $\kappa 3$ correlated with Ki-67. No significant correlation was found between ^{18}F-FLT and ^{11}C-MET uptake ratios and Ki-67. The authors concluded that "kinetic analysis of ^{18}F-FLT uptake is essential for the in vivo assessment of tumor proliferation in high-grade gliomas" and "might provide an accurate method for the assessment of early response to glioma treatment in the future."

Clinical Cancer Research

PET and APOEε4 Carriers

In a study published in the April issue of the *Journal of Alzheimers Disease* (2008;13:137–146), Rimajova et al. from Edith Cowan University (Joondalup, Australia) reported on preliminary data from studies designed to determine the extent of glucose hypometabolism in nonsymptomatic carriers of apoliprotein-ε4 (APOEε4). The study included 30 such participants (age range, 50–80 y) who underwent ^{18}F-FDG PET imaging and a neuropsychology assessment that included evaluation of subjective memory complaints. Neurologic soft signs were also assessed. Results were compared with a normative database. Glucose hypometabolism was seen in the study group in the anterior and posterior cingulate cortex and in the temporal association cortices, a pattern that was especially evident in APOEε4-heterozygous individuals. Although those with subjective memory complaints showed hypometabolism in these brain areas, those with no complaints showed no significant patterns of glucose hypometabolism. The authors concluded that levels of subjective memory complaints may be associated with Alzheimer's-related differences in regional cerebral glucose metabolism. An investigation in a larger patient population is planned.

Journal of Alzheimers Disease

PET and Language Activation Imaging

In the April issue of *Acta Oto-Laryngolica* (2008;128:393–397), Fuijwara et al. from the Kobe City Medical Center General Hospital (Japan) reported on the use of ^{18}F-FDG PET with a visual language task in children with profound deafness to explore cortical processing of the visual component of language and the effects of deafness on this activity. The study included 6 children who had lost their hearing before learning to speak and who had acquired varying levels of spoken communication skills. Each underwent PET imaging immediately after watching a video of the face of a speaking person. The cortical activity in each child was assessed and compared with activity in non-hearing-impaired individuals. The researchers found the widest bilaterally activated cortical area in the child who was least able to communicate with spoken language. They found no differences in cortical activation between the child who was the best user of spoken language and the group with normal hearing. They suggested that "this approach could help individuals involved in the habilitation and education of prelingually deafened children to decide upon the appropriate mode of communication."

Acta Oto-Laryngolica

^{123}I-MIBG Ties Cardiac and Parkinsonian Symptoms

In an article e-published on March 29 ahead of print in the *Journal of Neurological Sciences*, Kim et al. from the Catholic University of Korea (Seoul) reported on a study exploring the relationship between ^{123}I-metaiodiobenzylguanidine (^{123}I-MIBG) myocardial uptake and extent of Parkinsonian motor handicap in patients with minimal to severe disability. The study included 69 patients with Parkinson's disease who underwent ^{123}I-MIBG scintigraphy and clinical assessment while off medication. Tracer uptake was assessed using the ratio of the heart to the upper mediastinum (H/M ratio), and results were correlated with age, disease duration, and severity as measured by the modified Hoehn and Yahr stage and Unified Parkinson's Disease Rating Scale. A significant negative correlation was found between the H/M ratio and midline symptoms such as speech, posture, and gait difficulties. However, neither the severity metrics nor nonmidline symptoms were correlated with the degree of cardiac

sympathetic denervation. The authors concluded that this suggests "that the severity of midline motor symptoms is closely related to myocardial sympathetic dysfunction, although the implications of these findings require further study."

Journal of Neurological Sciences

THERAPY

RIT and Stem Cell Transplant in AML

In an article e-published on April 16 ahead of print in the *International Journal of Hematology*, Koenecke et al. from the Hannover Medical School (Germany) reported on radioimmunotherapy (RIT) with ^{188}Re-labeled anti-CD66 antibody in preconditioning for allogenic stem cell transplantation in high-risk acute myeloid leukemia (AML). The study included 21 patients (14 with high-risk AML; 6 with AML after myelodysplastic syndrome; and 1 with advanced myelodysplastic syndrome). All received the ^{188}Re-labeled anti-CD66 antibody in the conditioning regimen for allogeneic stem cell transplantation. Eleven patients proceeded to standard full-dose conditioning with busulfan and high-dose cyclophosphamide, and 10 patients proceeded to a reduced-intensity conditioning regimen. Patients received an unmanipulated allogeneic graft from alternative donors (15 patients) or a human leukocyte antigen–identical family donor (6 patients). Disease-free survival over a median follow-up of 42 mo was 43%. Treatment-related mortality was 28.6% (6 patients), and an additional 6 patients died of relapsing disease within 385 d of transplantation. At the time the article was submitted for publication, 9 patients were in complete hematologic remission. The authors concluded that in this challenging disease setting, "The combination of RIT with chemotherapeutic conditioning seems to be a therapy with an acceptable risk of treatment-related morbidity and mortality as well as occurrence of severe acute graft-versus-host disease."

International Journal of Hematology

ADEPT in Colon Cancer

Panjideh et al. from the Medizinische Klinik mit Schwerpunkt Hämatologie und Onkologie (Berlin, Germany) reported in the April issue of the *International Journal of Oncology* (2008;32:825–930) on in vitro and in vivo animal studies of the biodistribution and tumor targeting potential of antibody-directed enzyme-prodrug therapy (ADEPT), one of the many novel timed-sequence approaches in oncology. In ADEPT, an antibody-bound enzyme localizes to tumor tissue, where it selectively converts a subsequently administered nontoxic prodrug into a cytotoxic drug. In this study, the authors investigated ^{131}I-labeled A33scFv::CDy, a bifunctional fusion construct that includes a single chain antibody against the gpA33 antigen (highly expressed in colorectal cancers) and the prodrug-converting enzyme cytosine deaminase. The conjugate, when injected into mice bearing colon cancer xenografts, was found to have high uptake in tumors and low uptake in normal tissues, and specific binding was confirmed in in vitro assessments. Preliminary therapeutic studies also showed a significant reduction of tumor size in mice treated with the A33scFv::CDy-5-fluorocytosine/5-fluorouracil ADEPT system. The authors concluded that "^{131}I-A33scFv::CDy thus shows a biodistribution that makes it attractive for both radioimmunotherapy and ADEPT."

International Journal of Oncology

MOLECULAR IMAGING

Fluorescence Molecular Tomography and Bone Remodeling

Zilberman et al. from the Hadassah Medical Campus of Hebrew University (Jerusalem, Israel) reported in the April issue of the *Journal of Orthopaedic Research* (2008;26:522–530) on a small animal study assessing the use of fluorescence molecular tomography (FMT) for noninvasive visualization and quantification of nonunion fracture repair by genetically engineered mesenchymal stem cells. FMT is a near-infrared imaging modality that enables in vivo 3D quantitative determination of fluorochrome distribution in tissues at any depth in small animals. The researchers implanted murine mesenchymal stem cells overexpressing the osteogenic gene BMP2 into the thigh muscle and into a radial nonunion bone defect model in C3H/HeN mice. Real-time imaging of bone formation was performed after injection of a fluorescent bisphosphonate bone-imaging probe on d 7, 14, and 21 after cell implantation. All mice underwent micro-CT imaging to quantify bone formation at implantation sites. FMT detected higher fluorescent signals at the sites of the implants, and, at d 21, micro-CT indicated masses of mature bone formed in the implantation sites. The authors concluded that "These findings highlight the effectiveness of FMT as a functional platform for molecular imaging in the field of bone regeneration and tissue engineering."

Journal of Orthopaedic Research

hAADC Gene Therapy in Parkinson's Disease

In an article e-published on April 9 ahead of print in *Neurology*, Eberling et al. from the Lawrence Berkeley National Laboratory (CA), University of California (UC)–Davis, UC–San Francisco, and UC–Berkeley reported on the results of a phase 1 safety trial of human aromatic L-amino acid decarboxylase (hAADC) gene therapy for Parkinson's disease (PD). The group has previously published several studies in primate models of PD in which intrastriatal infusion of an adeno-associated viral (AAV) vector containing the hAADC gene resulted in robust gene expression. After gene transfer, low doses of levodopa were converted to dopamine in the transduced striatal neurons, resulting in behavioral improvement without the side effects usually associated with higher doses of the prodrug. The current safety study included 5 patients with moderate-to-advanced PD who received bilateral infusion of a low dose of the AAV-hAADC vector into the putamen. Each

patient underwent ^{18}F-fluoro-L-*m*-tyrosine (^{18}F-FMT) imaging at baseline and at 1 and 6 mo after infusion. PET indicated an average 30% increase in FMT uptake in the putamen after gene transfer, with evidence of sustained gene expression. Preliminary clinical data suggested modest improvement in symptoms, and the treatment was well tolerated. After this initial evidence of safety, the authors planned a second study with higher doses of the AAV-hAADC vector to determine whether escalating doses would produce corresponding clinical benefits.

Neurology

Hepsin-Targeted Imaging in Prostate Cancer

In the April issue of *Cancer Research*, Kelly et al. from the Massachusetts General Hospital and Harvard Medical School (Boston) reported on the development of hepsin imaging probes for early detection of prostate cancer. The researchers used phage display to isolate hepsin-binding peptides with 190 + 2.2 nmol/L affinity in monomeric form and high specificity. These peptides successfully detected human prostate cancer on tissue microarrays and in cell-based assays. Hepsin-targeted imaging agents were then synthesized by conjugating multiple peptides to fluorescent nanoparticles to improve pharmacokinetics and avidity. In initial studies in mice with xenografted prostate cancers, hepsin-targeted nanoparticles bound specifically to hepsin-expressing LNCaP xenografts. The authors concluded that hepsin imaging may provide a new method for early detection of prostate cancer.

Cancer Research

Minute Doses of $\alpha_v\beta_3$-Targeted Fumagillin Nanoparticles and Angiogenesis

In an article e-published on March 24 ahead of print in the *FASEB Journal*, Winter et al. from the Washington University Medical School (St. Louis, MO), Philips Medical Systems (Andover, MA), and Kereos, Inc. (St. Louis, MO), reported on the use of minute doses of $\alpha_v\beta_3$-targeted fumagillin nanoparticles to suppress the neovasculature and inhibit adenocarcinoma development in a rabbit model. Fumagillin is an antibiotic that has been shown to block angiogenesis in cancer models and clinical trials but is associated with neurotoxicity at systemic doses. On d 6, 9, and 12 after tumor implantation, rabbits were treated with $\alpha_v\beta_3$-targeted fumagillin nanoparticles, $\alpha_v\beta_3$-targeted nanoparticles without fumagillin, nontargeted fumagillin nanoparticles, or saline. On d 16 after implantation, each rabbit underwent MR imaging with $\alpha_v\beta_3$-targeted paramagnetic nanoparticles to assess tumor size and neovascularity. Tumor volume was found to be significantly reduced in the rabbits that received the $\alpha_v\beta_3$-targeted fumagillin nanoparticles compared with the other 3 treatment and control groups. MR imaging of control rabbits (those that received no fumagillin) showed a predominant peripheral distribution of neovascularity accounting for 7.2% of tumor rim volume compared with 2.8% in the group that received $\alpha_v\beta_3$-targeted fumagillin nanoparticles. Histology in tumor parenchyma showed T-cell infiltration after targeted fumagillin treatment, a phenomenon not seen in control animals. The authors concluded that these results suggest that "$\alpha_v\beta_3$-targeted fumagillin nanoparticles could provide a safe and effective means to deliver MetAP2 inhibitors alone or in combination with cytotoxic or immunotherapy."

FASEB Journal