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 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 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.

DIAGNOSIS

Dopamine Reward Pathways in ADHD

Volkow and colleagues from the National Institute on Drug Abuse (Bethesda, MD) and the Brookhaven National Laboratory (Upton, NY) reported in the September 9 issue of the *Journal of the American Medical Association* (2009;302:1084–1091) on the use of ^{11}C-raclopride and ^{11}C-cocaine PET imaging in evaluation of the biological bases underlying the reward/motivation deficit associated with attention-deficit/hyperactivity disorder (ADHD). The investigation focused on quantitative assessment of dopamine synaptic markers (transporters and D_2/D_3 receptors) in the brain dopamine reward pathway. The study included 53 nonmedicated adults with ADHD and 44 healthy controls. All participants underwent both ^{11}C-raclopride and ^{11}C-cocaine PET imaging for dopamine receptors and transporters, respectively. For both tracers, specific binding was lower in individuals with ADHD than in controls in areas of the dopamine reward pathway in the left side of the brain. Differences in the nucleus accumbens, midbrain, left caudate, and hypothalamic regions were calculated and validated. Analysis of these data led the authors to conclude that the reduction in dopamine synaptic markers associated with symptoms of inattention shown in the dopamine reward pathway in ADHD could have significant implications for development of novel diagnostic and therapeutic approaches in clinical management of the disorder.

Journal of the American Medical Association

SPECT in ADHD with Depression

In the September 1 issue of *Behavioral and Brain Functions* (2009;5:37), Gardner et al. from the Karolinska Institute (Stockholm, Sweden) and University Hospital Huddinge (Sweden) reported on a study using ^{99m}Tc-HMPAO SPECT to investigate the association between adult attention-deficit/hyperactivity disorder (ADHD) and depression. The study included 30 chronically depressed adult women who underwent assessments and were categorized as depressed (n = 16) and depressed with ADHD (n = 14). All participants, as well as 16 healthy women volunteers, underwent ^{99m}Tc-HMPAO SPECT and additional rating scale assessments. Analysis of images and assessments showed significant differences between the depressed, depressed with ADHD, and control groups. Mean scores in a well-validated depression rating scale were significantly lower in the depression group than in the depression with ADHD group, and tracer uptake was significantly decreased in the bilateral cerebellum in the depression with ADHD group but not in the depression group. Tracer uptake was also significantly increased in some bilateral frontal regions (Brodmann areas 8, 9, 10, 32) in the depression with ADHD group. When thalamic uptake was used in analysis along with scores from socialization and impulsivity scales, the researchers were able to discriminate among the 3 groups with 100% accuracy. The authors concluded that these findings "confirm the previous observation of a cerebellar involvement in ADHD" and that bilateral frontal uptake in ^{99m}Tc-HMPAO SPECT can differentiate between depression alone and depression associated with ADHD.

Behavioral and Brain Functions

ACE and ApoE Polymorphisms and Myocardial SPECT

In an article e-published on August 28 ahead of print in the *Journal of Human Genetics*, Georgoulias et al. from the University of Thessaly and University Hospital of Larissa (Greece) evaluated the correlation of angiotensin l-converting enzyme (ACE) and ApoE gene polymorphisms (E2, E3, E4, and g.-219G/T) with myocardial perfusion. The study included analysis of summed stress scores (SSS), summed rest scores (SRS), and summed difference scores (SDS) in 410 patients who underwent exercise–rest myocardial perfusion SPECT. Additional analyses showed that these variables differed significantly with patient genotype. Homozygotes for the ACE D allele had greater mean SSS and SDS values, and E3 homozygotes, E4 heterozygotes, and E4 homozygotes had significantly higher SSS and SDS values than E3 heterozygotes. E4 homozygotes had significantly higher SSS and SDS values than E3 homozygotes. For the g.-219G>T polymorphic site at the promoter region of the ApoE gene, mean values of SSS and SDS were significantly higher for T heterozygotes/homozygotes than for GG homozygotes. Over all, ACE D and both ApoE genotypes were found to be independent predictors that provided cumulative contributions in predicting SSS and

SDS. Moreover, each of the 3 genotypes was an independent predictor of abnormal SSS. The authors concluded that "these data provide the first evidence of an association and significant cumulative contribution of the aforementioned genotypes in myocardial perfusion, with the E4 allele having the strongest association followed by ACE D and ApoE g.-219T alleles."

Journal of Human Genetics

Stress MPI with Dual-Source Cardiac CTA

Blankstein et al. from the Massachusetts General Hospital and Harvard Medical School (Boston, MA) reported in the September 15 issue of the *Journal of the American College of Cardiology* (2009;54:1072–1084) on a study designed to determine the feasibility of performing a comprehensive cardiac CT examination combining stress and rest myocardial perfusion imaging (MPI) with dual-source coronary CT angiography (CTA). The study included 34 patients who underwent stress MPI and invasive angiography. The dual-source CT perfusion protocol included a contrast-enhanced scan during adenosine infusion, a contrast-enhanced rest CT using prospective triggering, and a delayed scan acquired 7 min after rest CT. All images were read independently. The dual-source CT perfusion protocol had a per-vessel sensitivity of 80% for detection of stenosis ≥ 50%, whereas SPECT MPI had a sensitivity of 67% and specificity of 83%. For detection of vessels with ≥ 50% stenosis with a corresponding SPECT perfusion abnormality, the CT protocol had a sensitivity of 93% and a specificity of 74%. The CT protocol during adenosine infusion had a per-vessel sensitivity of 96%, specificity of 73%, and negative predictive value of 98% for detection of stenosis ≥ 70%. The authors summarized their findings: "Adenosine stress CT can identify stress-induced myocardial perfusion defects with diagnostic accuracy comparable to SPECT, with similar radiation dose, and with the advantage of providing information on coronary stenosis."

Journal of the American College of Cardiology

Gait Disturbance and White Matter Changes

In an article e-published on September 18 ahead of print in *Neuroimage*, Iseki et al. from the Kyoto University Graduate School of Medicine (Japan) and the National Institutes of Neurological Disorders and Stroke (Bethesda, MD) reported on a study using MR and SPECT imaging assessment of cerebral perfusion to clarify the relationship between gait disturbances and age-related white matter changes (ARWMC). The study included 20 older individuals in whom extensive hyperintensities in the periventricular and deep white matter had been identified on T_2-weighted MR images. Clinical assessments were used to divide the group into gait-disturbed and non–gait-disturbed groups. All participants underwent treadmill gait analyses, with SPECT assessment of cerebral perfusion for both walking and rest states. In pooled data from all participants, gait-induced increases in cerebral perfusion were seen in the supplementary motor areas, lateral premotor cortex, primary motor and somatosensory areas, visual areas, basal ganglia, and cerebellum. A comparison of the 2 groups during gait-induced perfusion showed that the gait-disturbed group had relative underactivation of the supplementary motor areas, thalamus, and basal ganglia and relative overactivation of the premotor cortex. The authors concluded that these and other findings suggest that "abnormalities in the basal ganglia-thalamo-cortical loops partly explain gait disturbance observed in a subset of subjects with ARWMC."

Neuroimage

PET and CT in Pancreatic Cancer Relapse

Sperti et al. from the University of Padova (Italy) reported on September 24 ahead of print in the *Journal of Gastrointestinal Surgery* on a comparison of ^{18}F-FDG PET and CT in detection of tumor relapse after pancreatic cancer resection. The study included 72 patients who had previous surgery for pancreatic cancer and had undergone both ^{18}F-FDG and CT imaging for cancer recurrence. Patients were divided into 2 groups on the basis of imaging results: CT positive and CT nondiagnostic/PET positive. Disease progression and overall survival in the 2 groups were compared. Tumors recurred in 63 (87.5%) of the 72 patients, and PET directed 2 patients to resection of second cancers. Over all, tumor relapse was identified by CT in 35 patients and by PET in 61. Although PET influenced treatment strategies in 32 (44.4%) of 72 patients, the slightly longer average survival time in the CT nondiagnostic/PET positive group was not significant. Disease-free survival was similar in the 2 groups. The authors noted that the earlier diagnosis of recurrence by PET and its ability to influence treatment strategies did not benefit survival because of the current lack of effective therapies.

Journal of Gastrointestinal Surgery

PET in Autoimmune Pancreatitis

In an article e-published on September 2 ahead of print in the *Journal of Hepato-Biliary-Pancreatic Surgery*, Shigekawa et al. from the Aichi Cancer Center Hospital (Nagoya, Japan) reported on a study evaluating the utility of ^{18}F-FDG PET in estimating the efficacy of corticosteroid therapy in patients with autoimmune pancreatitis (AIP). The group focused on patterns of tracer accumulation in AIP and pancreatic cancer and evaluation of changes in uptake after steroid treatment. The study included 18 patients with AIP and 20 patients with PC who underwent PET imaging. ^{18}F-FDG uptake was seen in 88.9% of the AIP patients and 90.0% of the pancreatic cancer patients. Tracer uptake in salivary glands, eyes, and biliary ducts was seen only in AIP patients, and uptake in extra-abdominal lymph nodes was seen more frequently in AIP. Follow-up PET imaging after steroid therapy was performed in a subset of study partic-

ipants (6 AIP patients; 3 pancreatic cancer patients). Changes in maximized standardized uptake value after steroid therapy were estimated within 1 week in 5 AIP patients and in all 3 PC patients. In 4 AIP patients, the change was an increase of > 10%. For patients with pancreatic cancer, uptake remained unchanged or increased only slightly (< 10%). The authors concluded that patterns of ^{18}F-FDG uptake at baseline PET and a decrease in uptake after a short steroid trial "can be useful for discriminating AIP from pancreatic cancer."

Journal of Hepato-Biliary-Pancreatic Surgery

PET and Pancreatic Tumor Aggressiveness

Komar et al. from the University of Turku (Finland) reported in the September 1 issue of *Clinical Cancer Research* (2009;15:5511–5517) on the use of ^{15}O-water and ^{18}F-FDG PET/CT to assess blood flow and metabolism in normal pancreas and in different pancreatic lesions and to determine the effect of these imaging biomarkers on outcomes in patients with pancreatic cancer. The study included 26 patients being evaluated for possible pancreatic cancer who underwent ^{15}O-water and ^{18}F-FDG PET/CT imaging. Pancreatic blood flow and metabolism, as well as the ratio of standardized uptake value to blood flow (SUV/BF), were assessed. On the basis of imaging results, patients were divided into 3 groups: those with a finding of normal pancreas (n = 7), those with benign lesions (n = 8), and those with malignant tumors (n = 11). Patients with benign and malignant pancreatic tumors had 48% and 60% reductions, respectively, in blood flow in the lesion when compared with patients with normal pancreatic tissue. Maximum SUVs were 3 times higher in malignant tumors than in either benign lesions or normal pancreas. The SUV/BF was significantly higher in malignant than in benign lesions and in patients with normal pancreas tissue. A high SUV/BF in cancer patients was found to be a strong predictor of poor survival; high metabolism and lower-than-normal pancreatic blood flow were not. The authors noted that the compromised blood flow in pancreatic cancer may in part explain the poor success of radiotherapy and chemotherapy in this setting. They concluded by suggesting that "the composite measurement of blood flow and metabolism in pancreatic cancer could serve as a novel tool in the planning of treatments targeting vasculature."

Clinical Cancer Research

PET and TB Treatment

In an article e-published on September 8 ahead of print in *Antimicrobial Agents and Chemotherapy,* Davis et al. from the Johns Hopkins University School of Medicine (Baltimore, MD) reported on an animal study using ^{18}F-FDG PET to monitor response to 2 types of tuberculosis treatment. The study was conducted in BALB/c and C3HeB/FeJ mice models of *Mycobacterium* tuberculosis that were administered bactericidal (standard and highly active) or bacteriostatic drug regimens. Serial pulmonary PET images were compared with standard microbiologic methods to monitor treatment response. PET correctly identified the bactericidal activity of the drug regimens. Lesion-specific tracer activity also broadly correlated with treatment in C3HeB/FeJ mice that developed caseating lesions. The authors concluded that "Validated markers may also be useful as 'point-of-care' methods to monitor tuberculosis treatment in humans." The technique is also promising for drug development and assessment, with fewer animals required and results available in real time rather than after colony-forming laboratory procedures.

Antimicrobial Agents and Chemotherapy

MOLECULAR IMAGING AND THERAPY

Quadruple Imaging Modality with Nanoparticles

Hwang Do et al. from the Seoul National University College of Medicine (Republic of Korea) reported in the September 21 issue of *Chemistry* (2009;15:9387–9393) on a multimodal nanoparticle imaging system capable of concurrent fluorescence, bioluminescence resonance energy transfer, PET, and MR imaging in small animal studies. They described the development of a cobalt–ferrite nanoparticle surrounded by rhodamine conjugated with luciferase and p-SCN-bn-NOTA, with the addition of $^{68}GaCl_3$. In vitro studies showed that the nanoparticles transfected well into cells and that the activity of each of the 4 imaging modalities increased as the number of nanoparticles in cells increased. In vivo studies also showed intense target activity in mice administered the nanoparticles. The authors concluded that this multimodal imaging strategy could have great promise in tracking cells and monitoring therapy.

Chemistry

Targeting and Purging Metastases in SLNs

In the September issue of the *Journal of Biophotonics* (2009;2:528–529), Galanzha et al. from the University of Arkansas for Medical Sciences (Little Rock) introduced a novel diagnostic and therapeutic fiber-based portable device for in vivo noninvasive detection and treatment of metastases in sentinel lymph nodes (SLNs) at the single-cell level. The researchers used an integrated system of multicolor photoacoustic (PA) lymph flow cytometry, PA lymphography, absorption image cytometry, and photothermal therapy in a melanoma-bearing mouse model of breast cancer. They demonstrated the capability of this platform for real-time lymphatic mapping, counting of disseminated tumor cells in prenodal lymphatics, detection of metastasis in SLNs, and purging of these metastases. Nanoparticles were used to label, detect, and ablate nonpigmented breast cancer cells in SLNs. The authors concluded that the "association between disseminated tumor cell count and SLN metastasis progression supports lymphatic disseminated tumor

cells as a novel prognostic marker of metastasis" and that "the fiber-based portable PA device may replace the conventional SLN excision and histology-based staging."

Journal of Biophotonics

Optical–Radionuclide Imaging of Caspase-3 Activity

Lee et al. from the Washington University School of Medicine (St. Louis, MO) reported in the July/August issue of the *Journal of Biomedical Optics* (2009;14:040507) on a new multimodal optical–nuclear molecular probe (^{64}Cu-LS498) with complementary reporting strategies based on the capability of modulating fluorescence intensity by specific molecular events. The probe was made with tetraazacyclododecanetetraacetic acid for chelating a radionuclide (^{64}Cu), a near-infrared fluorescent dye, and an efficient quencher dye. The authors described the development of the probe and initial enzyme kinetics studies. Using the ^{64}Cu-LS498 probe in a controlled and localized in vivo mouse model of caspase-3 activation, a time-dependent 5-fold near-infrared fluorescence enhancement was observed, whereas radioactivity remained identical in caspase-3–positive animals and in caspase-3–negative controls. The authors concluded that "these results demonstrate the feasibility of using radionuclide imaging for localizing and quantifying the distribution of molecular probes and optical imaging for reporting the functional status of diagnostic enzymes."

Journal of Biomedical Optics

MR in High-Functioning Autism

Sahyoun et al. from the Massachusetts General Hospital (Charlestown) and the Harvard–Massachusetts Institute of Technology Division of Health Sciences and Technology (Cambridge) reported on August 19 ahead of print in *Neuropsychologia* on MR and diffusion tensor neuroimaging of the functional and structural networks underlying visuospatial and linguistic reasoning in children with high-functioning autism. The study included 12 children with high-functioning autism and 12 age- and IQ-matched typically developing control children. All participants were assessed with MR and diffusion tensor imaging while performing 3 types of pictorial reading paradigms: 1 requiring visuospatial processing, 1 requiring language (semantic) processing, and 1 requiring hybrid skills in which language use could facilitate visuospatial transformations. MR imaging indicated that activated areas were similar in the brains of the 2 groups. The two groups showed similar networks, with linguistic processing activating inferior frontal, superior and middle temporal, ventral visual, and temporoparietal areas, whereas visuospatial processing activated occipital and inferior parietal cortices. Occipitoparietal and ventral temporal areas appeared to be more activated in high-functioning autism, whereas the control group relied more on frontal and temporal language regions. A clinically observed increased reliance on visuospatial abilities in high-functioning autism was supported by intact connections between inferior parietal and ventral temporal regions of interest. In addition, the inferior frontal region showed reduced connectivity to ventral temporal and middle temporal areas in high-functioning autism, reflecting impaired activation of frontal language areas. The authors concluded that the high-functioning autism group's "engagement of posterior brain regions along with weak connections to frontal language areas suggest support for a reliance on visual mediation in autism, even in tasks of higher cognition."

Neuropsychologia

Platelet Targeting by Cyclic RGD-Modified Liposomes

In an article e-published on September 9 ahead of print in the *Journal of Biomedical Materials Research, Part A*, Srinivasan et al. from the Case Western Reserve University (Cleveland, OH) reported on in vitro and in vivo platelet targeting by cyclic RGD-modified liposomes. They described the development of liposome nanoparticles surface-modified by RGD peptide ligands with targeting specificity to the integrin GPIIb-IIIa, which is upregulated and stimulated into a ligand-binding conformation on surface-activated platelets. These platelet-targeted nanoparticles hold the promise of vascular site-selective delivery of drugs and imaging probes. The authors detailed in vitro studies to verify successful platelet-targeting by the peptide-modified liposomes and in vivo studies in which liposomes were introduced in a catheter-injured carotid artery restenosis model in rats. Both fluorescence microscopy and scanning electron microscopy were used to verify results. The authors concluded that these results "validate our nanoparticle design for site-selective vascular delivery."

Journal of Biomedical Materials Research, Part A

SPECT/CT and Chemotherapy in NSCLC

Yang et al. from the Netherlands Cancer Institute–Anton van Leeuwenhoek Hospital (Amsterdam) reported on September 12 ahead of print in *Molecular Imaging and Biology* on a study designed to examine the prognostic value of prechemotherapy ^{99m}Tc-MIBI SPECT in relation to tumor size change measured by CT in patients with non–small cell lung cancer (NSCLC). The study included 11 patients with stage IIIB/IV NSCLC who underwent ^{99m}Tc-MIBI SPECT/CT in the 24-h period before initiation of platinum-containing chemotherapy. Using Response Evaluation Criteria in Solid Tumors criteria, 20 lesions from the 11 patients were available for evaluation, and maximum and mean activity ^{99m}Tc-MIBI counts were calculated for each of these. CT measurements of lesions were made by experts, and assessment of response was made on CT after 2 cycles of chemotherapy. A significant correlation was found between mean ^{99m}Tc-MIBI activity and change in the longest diameter of

the target lesion. Mean ^{99m}Tc-MIBI activity also correlated negatively with change in the area of the largest transverse surface of the target lesion. The authors concluded that their series "demonstrated solid, negative correlations between prechemotherapy ^{99m}Tc-MIBI uptake and tumor size change measured by CT for advanced NSCLC," a finding that could have strong implications for new imaging protocols and treatment strategies in this patient group.

Molecular Imaging and Biology

MR and Sunitib in Renal Cell Carcinoma

In an article published in the September issue of *Neoplasia* (2009;11: 910–920), Hillman et al. from the Wayne State University School of Medicine (Detroit, MI) reported on dynamic contrast-enhanced MR imaging of antiangiogenic changes induced by sunitinib in papillary renal cell carcinoma xenografts. The study focused on an orthotopic KCI-18 model of human renal cell cancer xenografts in nude mice treated with various doses of sunitinib, followed by dynamic contrast-enhanced MR imaging and histologic studies. Sunitinib was found to induce dose-dependent vascular changes in kidney tumors and in normal kidneys. A dosage of 10 mg/kg/d caused mild changes in gadolinium uptake and clearance kinetics in kidney tumors. A dosage of 40 mg/kg/d induced increased vascular tumor permeability with gadolinium retention, which the authors attributed to destruction of tumor vasculature. This higher dosage also caused vascular alterations of normal vessels. Sunitinib at 20 mg/kg/d caused increased tumor perfusion and decreased the vascular permeability associated with thinning and regularization of tumor vessels while only mildly affecting normal vessels. Alterations in tumor vasculature were found to result in a significant inhibition of KCI-18 tumor growth at dosages of 20 and 40 mg/kg/d. In vitro studies showed that sunitinib also had direct cytotoxic effects in KCI-18 cells. The authors concluded that "these data suggest that a sunitinib dosage of 20 mg/kg per day, which inhibits renal cell carcinoma tumor growth and regularizes tumor vessels with milder effects on normal vessels, could be used to improve blood flow for combination with chemotherapy."

Neoplasia

(Continued from page 19N)

21 the award of 3 grants to stimulate the development and availability of medical devices for children. A panel of 6 experts with experience in medicine, business, and device development reviewed 16 applications for the grants, which will be administered by the FDA Office of Orphan Products Development. The recipients and grant amounts include: James Geiger, MD, and the Michigan Pediatric Device Consortium, $1 million; Pedro DelNido, MD, and the Pediatric Cardiovascular Device Consortium, $500,000; and Michael Harrison, MD, and the University of California at San Francisco Pediatric Device Consortium, $500,000.

The FDA noted that development of medical devices for children lags up to a decade behind similar devices intended for use in adults. Children differ among themselves and from adults in terms of size, growth, and body chemistry and present unique challenges to device designers. In addition, the activity level and ability to manage some implantable or long-term devices may vary greatly among children.

"Congress provided the FDA with this funding so that we could help connect innovators and their ideas with experienced professionals who assist them through development" said Timothy Cote, director of the FDA Office of Orphan Product Development. "These grants will strengthen public health by spurring the development of medical devices that safely and effectively meet the special and unique needs of our children."

Those receiving the grants will encourage innovation and connect qualified individuals with good pediatric device ideas to potential manufacturers; mentor and manage pediatric device projects through their development, including prototype design and marketing; connect innovators and physicians to existing federal and nonfederal resources; and assess the scientific and medical merit of proposed pediatric projects and provide assistance and advice on business development, training, prototype development, and postmarketing needs. Each of the grant recipients will coordinate among the FDA, device companies, and the National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Human Development to facilitate research and any necessary applications for device approval or clearance.

U.S. Food and Drug Administration
Centers for Medicare & Medicaid Services