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.

MOLECULAR IMAGING AND THERAPY

Improved Nanoparticles for Cardiac MR

In the May issue of the *Journal of the American College of Cardiology, Cardiovascular Imaging* (2009;2:637–547), Lipinski et al. from the Mount Sinai Medical Center (New York, NY) reported on development and initial studies of gadolinium-containing lipid-based nanoparticles that target the macrophage scavenger receptor-B (CD36) for use in cardiac MR detection and characterization of human atherosclerosis. Studies were conducted in human aortic specimens acquired at autopsy. Three types of nanoparticles (gadolinium-containing but untargeted, anti-CD36, and nonspecific) were incubated in the specimens. T1, T2, and proton density-weighted 3-dimensional scans were performed, and results were compared with immunohistopathology. Confocal microscopy and inductively coupled plasma mass spectroscopy showed in vitro macrophage uptake of targeted nanoparticles but minimal uptake of nontargeted particles. Targeted nanoparticles increased contrast-to-noise ratio in T1 imaging by 52.5%, significantly greater than in the nonspecific or nontargeted particles. Additional analyses verified that the anti-CD36 nanoparticles targeted resident macrophages, but the untargeted and nonspecific particles were found diffusely throughout the plaque. The authors concluded that "macrophage-specific (CD36) nanoparticles bind human macrophages and improve cardiac MR detection and characterization of human aortic atherosclerosis" and help identify high-risk human plaque before an atherothrombotic event.

Journal of the American College of Cardiology, Cardiovascular Imaging

Quantum Dots for Prostate Cancer Micrometastases

In an article e-published on May 8 ahead of print in *Urology*, Shi and colleagues from Emory University School of Medicine (Atlanta, GA) and the Third Military Medical University (Chongqing, China) reported on the use of bioconjugated near-infrared fluorescent quantum dot probes to visualize human prostate cancer cells in the skeletons of living mice. In vitro and in vivo studies of human prostate cancer C4-2B xenografts grown in mouse tibia verified visualization by prostate-specific membrane antigen antibody conjugated with quantum dots emitting light in the near-infrared range of 800 nm. They found that as few as 5,000 cells could be detected when tagged with QD800 conjugate and injected subcutaneously into mice. When injected intravenously into mice with C4-2B tumors in tibia, signal could be detected from a minimum of 500,000 cells. Maximum visualization was achieved 30 min after intravenous injection of the conjugate. The authors concluded that these animal studies suggest that "bioconjugated near-infrared quantum dot probes are highly sensitive molecular imaging tools for human prostate cancer micrometastases in mice."

Urology

Carbon Nanotube–Enhanced Photoacoustic SLN Mapping

In the June issue of *Physics in Medicine and Biology* (2009;54:3291–3301), Pramanik et al. from Washington University (St. Louis, MO) reported on carbon nanotube–enhanced noninvasive photoacoustic mapping of sentinel lymph nodes. The authors described initial studies with a single-walled carbon nanotube and photoacoustic imaging in a rat model that produced high contrast-to-noise ratios and good resolution (~500 μm). In addition, the nanotubes showed optical characteristics that maximize imaging depth in areas where biological tissues (hemoglobin, tissue pigments, lipids, and water) had low light absorption. They concluded that in the future "functionalization of the single-walled nanotubes with targeting groups should allow the molecular imaging of breast cancer."

Physics in Medicine and Biology

Near-Infrared Spectroscopy in Carotid Artery Stenting

Matsumoto et al. from the Kokura Memorial Hospital (Kitakyushu, Japan) reported in the April 28 issue of *Neurology* (2009;72:1512–1518) on the use of transcranial near-infrared spectroscopy for noninvasive monitoring of regional cerebral oxygen saturation as a predictor of cerebral hyperperfusion syndrome after carotid artery stenting. The study included 64 patients (52 men, 12 women) whose regional cerebral oxygen saturation was monitored with near-infrared spectroscopy during the

carotid stenting procedure. Cerebral hyperperfusion syndrome was diagnosed in 2 patients (3.1%) on the day after the procedure on the basis of increased cerebral blood flow on SPECT and deterioration of neurologic symptoms. In these 2 patients, postreperfusion regional cerebral oxygen saturation values increased >24% from baseline until 3 min after reperfusion in the stenting procedure. In the remaining patients, the normal upper limit of the regional cerebral oxygen saturation change averaged 10.0% at 3 min after reperfusion. The authors concluded from this relatively small dataset that in "patients showing a regional cerebral oxygen saturation at 3 min after reperfusion increased by more than 10.0%, cerebral hyperperfusion syndrome following carotid artery stenting could be predicted" and that near-infrared spectroscopy can provide valuable noninvasive information in this setting.

Neurology

Novel Conjugates for Imaging VEGF Receptors

In an article e-published on May 7 ahead of print in the *Journal of Biomedical Materials Research. Part A*, Lee et al. from the Chonbuk National University Medical School and Hospital (Jeonju, Republic of Korea) reported on an investigation of the ability of either ^{99m}Tc- or Cy5.5-labeled chitosan-DC101 conjugates to identify vascular endothelial growth factor receptor 2 (VEGFR-2) overexpressed in ischemia. Initial in vitro cell binding studies were performed to evaluate targeting of the conjugates, followed by γ and optical imaging in a mouse hindlimb model of ischemia. At 2, 12, and 24 h after creation of ischemia, the ^{99m}Tc- or Cy5.5-labeled chitosan-DC101 conjugates were injected into the mice, with γ and optical imaging following injections by 1 or 3 h. Both types of imaging showed higher uptake in ischemic muscles, with scintigraphy data indicating that the ischemic-to-contralateral-limb ratio of uptake was 4.5 ± 0.25 at 24 h after surgery. The authors concluded that both ^{99m}Tc- and Cy5.5-labeled chitosan-DC101 conjugates "have the potential to be useful as VEGFR-2-targeted imaging agents for monitoring ischemia."

Journal of Biomedical Materials Research. Part A

Visualizing Cancer Gene Therapy

In an article e-published on May 21 ahead of print in *Gene Therapy*, Aung et al. from the National Institute of Radiological Sciences (Chiba, Japan) reported on the use of optical and high-field MR imaging for in vivo visualization of electroporation-mediated transgene expression in experimental tumors. They described the development of a dual-reporter plasmid carrying a gene-encoding MR reporter ferritin heavy chain and red fluorescent protein gene. After promising in vitro studies with transfected cells, the plasmid was injected into experimental tumors. The result was both fluorescent emissions on optical imaging and lowered signal on T2 MR. Immunohistologic analyses confirmed that both of the reporter transgenes were expressed in the injected area. The authors concluded that this strategy "provides a platform for evaluating electroporation-mediated cancer gene therapy easily and safely without administering contrast agent or substrate."

Gene Therapy

THERAPY

RIT in Microscopic Liver Mets of Colorectal Origin

In an article e-published on May 9 ahead of print in the *Annals of Surgical Oncology*, de Jong et al. from the Radboud University Nijmegen Medical Center (The Netherlands) described a study assessing the efficacy of radioimmunotherapy (RIT) with a radiolabeled monoclonal antibody (mAb) in experimental colorectal liver metastases. The study was performed in rats injected with CC531 tumor cells. RIT was administered as ^{111}In-labeled MG1 mAb or an isotype-matched control antibody (^{111}In-UPC-10) on either the day of tumor inoculation or 14 d later. A separate control group received saline only. The ^{111}In-labeled MG1 mAb accumulated preferentially in liver tumors, and ^{111}In-UPC-10 did not. Administration of the 2 agents showed no significant side effects. ^{177}Lu-MG1 RIT administered immediately after surgery improved survival significantly compared with administration of ^{177}Lu-UPC-10 at that time point. However, improved survival was not seen when treatment was delayed to 14 d. The authors concluded that "this study provides proof of principle that RIT can be an effective treatment modality for microscopic liver metastases, whereas RIT is not effective in larger tumors."

Annals of Surgical Oncology

^{90}Y Microspheres in Colorectal Hepatic Metastases

Mulcahy et al. from Northwestern University (Chicago, IL) reported in the May 1 issue of *Cancer* (2009;115:1849–1858) on a study to determine the safety and efficacy of ^{90}Y microsphere treatment in patients with liver-dominant colorectal metastases. The study included 72 patients with unresectable hepatic colorectal metastases who underwent ^{90}Y microsphere treatment at a targeted absorbed dose of 120 Gy. Safety and toxicity were assessed, and PET and CT were used to evaluate response. Treatment-related toxicities included fatigue (61%), nausea (21%), abdominal pain (25%), and grades 3 and 4 bilirubin toxicities (12.6%). The tumor response rate was 40.3%, with PET assessing a response rate of 77%. Overall survival from the date of initial hepatic metastases averaged 34.6 mo. The median time to hepatic progression after RIT was 15.4 mo. Less than 25% tumor replacement was associated with significantly greater median survival, and, as expected, extrahepatic disease at the time of treatment was associated negatively with overall survival. The authors concluded that ^{90}Y microsphere therapy "appears to provide sustained disease

stabilization with acceptable toxicity" and that "asymptomatic patients with preserved liver function at the time of ^{90}Y appeared to benefit most from treatment."

Cancer

Refining Anti-CD22 Immunotherapy

In an article e-published on May 13 ahead of print in *Cancer Immunology, Immunotherapy*, O'Donnell et al. from the University of California, Davis, Cancer Center (Sacramento) reported on a study designed to identify optimal timing, scheduling, and choice of targeted epitope for anti-CD22 immunotherapy in mice bearing human lymphoma xenografts. The study focused on the effects of HB22.7, an anti-CD22 mAb that binds the 2 NH_2-terminal immunoglobulin domains and blocks the interaction of CD22 with its ligand, inducing apoptosis in neoplastic B-cells and offering a promising treatment strategy for non-Hodgkin lymphoma (NHL). Raji NHL-bearing nude mice were administered either the HB22.7 or nonblocking anti-CD22 mAb control agent. HB22.7 improved survival significantly and shrank tumors substantially, whereas the control agent did not. Smaller tumors ($<$200 mm^3) showed a higher response rate than larger tumors. Additional data provided by the study included optimal dose, route, and dosage schedules. In addition, PET imaging of ^{64}Cu-labeled HB22.7 verified that NHL was rapidly and specifically targeted.

Cancer Immunology, Immunotherapy

DIAGNOSIS

PET, CSF, and Preclinical Alzheimer's Disease

Two articles published in May addressed the relationship between changes in cerebral glucose metabolism as assessed by PET and specific alterations in cerebrospinal fluid (CSF), both of which are associated with presymptomatic onset of Alzheimer's disease. Petrie et al. from the Veterans Affairs Puget Sound Health Care System (Seattle, WA) reported in the May issue of *Archives of Neurology* (2009;66:632–637) on a study designed to assess whether cerebral glucose metabolism and CSF levels of τ and β-amyloid peptide 42 in healthy individuals correlate in brain structures affected early in Alzheimer's. The study included 20 healthy individuals without dementia (age range, 46–83 y) who underwent lumbar CSF sampling (for assessment of β-amyloid peptide 1-42, τ, and τ phosphorylated at threonine 181 [pτ-81] levels) and ^{18}F-FDG PET imaging. In the posterior cingulate, precuneus, and parahippocampal regions significant negative correlation was found between cerebral glucose metabolism and CSF τ and pτ-81 levels. A limited positive correlation was found between cerebral glucose metabolism and CSF β-amyloid peptide levels in the inferior temporal cortex and the parahippocampal gyrus. A negative association was also found between cerebral glucose metabolism and CSF τ and pτ-81 levels in the parietal and medial parietal lobes. These results, with higher CSF τ and pτ-81 concentrations associated with more severe hypometabolism in several brain regions affected very early in AD and lower CSF β-amyloid peptide 1-42 concentrations associated with hypometabolism in only the medial temporal lobe, suggested to the authors that "early τ and β-amyloid abnormalities may be associated with subtle synaptic changes in brain regions vulnerable to Alzheimer's disease." They cited the need for a longitudinal assessment of CSF and PET biomarkers to determine the extent to which these changes can predict the onset of cognitive impairment.

Vukovich et al. from the Technische Universität München (Germany) reported in the May issue of *Dementia and Geriatric Cognitive Disorders* (2009; 27:474–480) on investigation of the same brain correlates of metabolism and CSF levels in 32 patients with mild-to-moderate Alzheimer's disease. These patients underwent ^{18}F-FDG PET imaging for cerebral glucose metabolism assessment and CSF analyses of τ protein and β-amyloid 42 levels. A strong positive correlation was identified between CSF β-amyloid 42 levels and glucose metabolism in 2 extensive clusters in the right temporal, prefrontal, and anterior cingulate cortices. No association was found between glucose metabolism and τ protein levels in any brain region. The authors concluded that these findings "point to a significant association between synaptic dysfunction as measured with ^{18}F-FDG PET and CSF β-amyloid 42, but do not suggest a correlation between synaptic function and CSF τ levels."

Archives of Neurology
Dementia and Geriatric Cognitive Disorders

Imaging Transient LV Dysfunction Syndrome

In an article e-published on May 12 ahead of print in the *International Journal of Cardiology,* Cimarelli et al. from the Hôpitaux Universitaires de Strasbourg (France) reported on nuclear medical imaging to elucidate the underlying mechanisms of transient left ventricular dysfunction syndrome (TLVDS). The study included 18 patients with TLVDS (13 with Takotsubo cardiomyopathy and 5 with midventricular ballooning syndrome) who underent myocardial ^{99m}Tc-tetrofosmin or ^{201}Tl gated SPECT (n = 11), ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) SPECT (n = 8), and/or ^{18}F-FDG gated PET (n = 15) to assess LV perfusion, sympathetic innervation, and glucose metabolism, respectively. Results indicated that hypocontractile LV segments were characterized by normal perfusion but reduced ^{123}I-MIBG and ^{18}F-FDG uptake. Follow-up ^{123}I-MIBG SPECT and ^{18}F-FDG PET in a subset of patients showed rapid normalization of LV motion and progressive improvement of both glucose metabolism and sympathetic innervation. The authors observed that if neurogenic myocardium stunning is hypothesized as the central causative mechanism of TLVDS, then ^{123}I-MIBG SPECT seems to be the most specific diagnostic approach and that nuclear imaging can play a key role

in exploring the pathophysiologic mechanisms of the syndrome.

International Journal of Cardiology

Intramyocardial Cell Therapy

Two studies appearing in the medical literature in May addressed the efficacy of intracardiac cell therapy to improve cardiac function, as well as the ability of nuclear medicine imaging to monitor this treatment. van Ramshorst et al. from the Leiden University Medical Center (The Netherlands) reported in the May 20 issue of the *Journal of the American Medical Association* (2009;301:1997–2004) on a study exploring the value of intramyocardial bone marrow cell injection in improving chronic myocardial ischemia and impaired left ventricular (LV) function. The randomized, double-blind trial included 50 patients (43 men, 7 women; mean age, 64 y) with chronic myocardial ischemia and severe angina pectoris despite optimal medical therapy who were ineligible for conventional revascularization. Patients received intramyocardial injection of autologous bone marrow-derived mononuclear cells or placebo solution and were followed at 3 and 6 mo with several assessments, including a 17-segment score for stress myocardial perfusion as quantified by ^{99m}Tc-tetrofosmin SPECT, LV ejection fractions (LVEF), Canadian Cardiovascular Society (CCS) class, and Seattle Angina Questionnaire quality-of-life score. A subset of patients also underwent cardiac MR imaging. At 3-mo follow-up, the summed stress scores of patients in the group that received bone marrow cells improved from a mean of 23.5 to 20.1, whereas the scores of those in the placebo group decreased from 24.8 to 23.7. MR imaging indicated a 3% absolute increase in LVEF at 3 mo in treated patients, with no corresponding improvement in the placebo group. CCS angina scores and quality-of-life scores increased significantly at 6 mo for bone marrow cell–treated patients. The authors concluded that although "intramyocardial bone marrow cell injection resulted in a statistically significant but modest improvement in myocardial perfusion compared with placebo," additional studies should be performed to assess long-term effects and outcomes.

In an article e-published on May 12 ahead of print in the *International Journal of Cardiology*, Alt et al. from the Tulane University Health Sciences Center (New Orleans, LA) and the University of Texas M.D. Anderson Cancer Center (Houston, TX) reported on the effect of intracoronary administration of freshly isolated autologous tissue resident stromal cells on cardiac function and perfusion after acute myocardial infarction in a porcine model. Freshly isolated, uncultured autologous stromal cells or control solution was injected into the infarcted artery at the time of reperfusion in pigs with induced myocardial infarction. Animals then underwent ^{99m}Tc-SPECT at baseline and 8 wk to assess cardiac function and area at risk. At 8 wk, pigs treated with stromal cells showed a 20% smaller myocardial perfusion defect than animals that received the placebo. This reduction in perfusion defect was associated with a significantly higher myocardial salvage index in the treated group as well as a significant increase in ejection fraction. This functional improvement in the treated group was also reflected by greater wall thickness in the infarct and border zone and increased capillary density in the border zone. The authors concluded that this study demonstrated that "recovery and intracoronary delivery of uncultured autologous tissue–derived stromal cells at time of vessel reperfusion is feasible and improves ventricular function."

Journal of the American Medical Association
International Journal of Cardiology

3D Surface Projection SPECT in Parkinson's Disease

In an article e-published on May 13 ahead of print in *Movement Disorders*, Osaki et al. from the Kochi Medical School (Nankoku, Japan) reported on cross-sectional and longitudinal studies of 3-dimensional stereotactic surface projection SPECT analysis to explore the pathologic substrates of increasing dementia in Parkinson's disease. The study began with SPECT and other data from 55 patients originally diagnosed with Parkinson's disease who were imaged in the cross-sectional study. This study indicated that patients with Parkinson's disease and dementia had significantly reduced perfusion in the right posterior cingulate, right precuneus, and left posterior cingulate areas. A subset of 21 patients (12 with and 9 without dementia) was enrolled in the longitudinal study to assess perfusion changes over the course of their disease. In this part of the study, significantly reduced perfusion was observed in the left anterior frontal gyrus in patients without dementia and in the right inferior parietal lobule in those who developed dementia. These findings suggested to the authors a relationship between developing dementia in Parkinson's disease and reduced perfusion in the posterior parietal area.

Movement Disorders

PET in Persistent Lyme Encephalopathy

Fallon and colleagues from the College of Physicians and Surgeons of Columbia University (New York, NY) reported in the May issue of the *Archives of General Psychiatry* (2009;66:554–563) on a study designed to explore patterns in abnormalities in global or topographic distributions of regional cerebral blood flow (rCBF) or cerebral metabolic rate (rCMR) in patients with a history of well-characterized Lyme disease and persistent cognitive deficit. The study included 17 healthy matched volunteers and 35 patients with well--documented prior Lyme disease, currently reactive IgG Western blot, prior treatment with at least 3 wk of intravenous cephalosporin, and objective memory impairment. All participants underwent PET imaging. CBF was assessed in 2 resting room conditions (with and without snorkel) and 1 challenge condition (room air enhanced with carbon dioxide [hypercapnia]). Statistical parametric mapping analyses

of imaging results showed consistent regional abnormalities in rCBF and rCMR measurements in the Lyme group, primarily indicating hypoactivity. Among these abnormalities were deficits in bilateral gray and white matter regions, mainly in the temporal, parietal, and limbic areas. Additional data suggested that these regional abnormalities were primarily metabolically driven. No significant differences were identified in global resting CBF and CMR measurements in patients and volunteers. The authors concluded that the presence of objectively quantifiable topographic abnormalities in functional brain activity in patients with persistent Lyme encephalopathy points to the need for additional studies to determine whether this pattern also characterizes the disease in the acute neurologic stage.

Archives of General Psychiatry

PTH Evaluation on Fine-Needle Washing After Aspiration Biopsy

Giusti et al. from San Martino University Hospital (Genoa, Italy) reported in the May issue of the *Journal of Zhejiang University. Science. B.* on an evaluation of the technique in which parathyroid hormone (PTH) is assayed in the washing liquid after fine-needle aspiration biopsy (FNAB) as a means to locate parathyroid tissue. The study included 47 patients with a clinical diagnosis of primary hyperparathyroidism and ultrasound studies suggestive of a parathyroid lesion who underwent PTH FNAB. Patients were divided into 2 groups on the basis of the absence or presence of thyroid alterations on ultrasound. PTH FNAB results were compared with those from cytology, scintigraphy, and surgical outcomes in those 24 patients who proceeded to surgery. Cytology was diagnostic for benign thyroid lesions and nondiagnostic for thyroid lesions, hyperplastic parathyroid tissue, undetermined or malignant thyroid lesions, and other lesions in 45%, 30%, 17%, 4%, and 4% of cases, respectively. In 47% of patients, PTH FNAB confirmed accurately that the sample had been obtained in parathyroid tissue. The diagnostic accuracy of PTH FNAB was greater than that of scintigraphy in patients without thyroid abnormalities on ultrasound. After surgery, the positive predictive value and sensitivity were 94% and 83%, respectively, for FNAB and 71% and 69%, respectively, for scintigraphy. The authors concluded that PTH evaluation after FNAB appears to be more diagnostic than cytology and scintigraphy and may be the "method of choice when the target is ultrasound suggestive and reachable," as well as a promising method for guiding surgical intervention.

Journal of Zhejiang University. Science. B.

Delayed Gastric Emptying in Diabetic Gastroparesis

In an article e-published on Apri 30 ahead of print in *Gastroenterology*, Hyett et al. from the Brigham and Women's Hospital (Boston, MA) reported on the ability of gastric emptying studies to predict morbidity and mortality associated with diabetic gastroparesis. The study included 3 groups: group A (n = 94), diabetics (type 1 and type 2) with classic symptoms of gastroparesis (early satiety, postprandial fullness, bloating, abdominal swelling, nausea, vomiting, and retching) and delay in radionucleotide gastric emptying study; group B (n = 94), diabetics with classic symptoms of gastroparesis but negative scintigraphy; and group C (n= 94), diabetics without symptoms of gastroparesis. Data points included number of days hospitalized and number of hospitalizations, office visits, emergency department (ED) visits; death rate; glycosylated hemoglobin levels; medications; and past medical history. Group A was found to have significantly more hospital days per 1,000 patient d (25.5 d) than groups B or C (5.1 and 2.3 d, respectively). Group A also had significantly greater numbers of hospitalizations, office visits, and ED visits than the other 2 groups. Group A patients were also more likely to have cardiovascular disease, hypertension, and retinopathy. Deaths and glycosylated hemoglobin levels did not differ among the 3 groups. The authors concluded that "a delayed radionucleotide gastric emptying study predicts negative health outcomes in diabetics with symptoms of gastroparesis" and that this correlation between diabetic gastroparesis and cardiovascular disease, hypertension, and retinopathy may indicate an underlying vascular etiology.

Gastroenterology

PET/CT in Subclinical Inflammation and Ulcerative Colitis

Rubin et al. from the University of Chicago Medical Center (IL) reported in the May issue of *Inflammatory Bowel Diseases* (2009;15:750–755) on a study designed to assess the limits of PET/CT technology in assessing inflammatory activity in patients with nonactive ulcerative colitis. The study included 10 patients (6 male, 2 female; 8 with pancolitis, 1 with extensive colitis, 1 with proctosigmoiditis), with a median disease duration of 32 y. All participants underwent ^{18}F-FDG PET/CT imaging at a mean of 37 d after endoscopy. Uptake was assessed in each of 4 colonic segments on a 3-point scale. On PET imaging, 6 patients showed no increased tracer uptake and 3 had increased uptake in the rectosigmoid segment. One patient with uptake in the rectosigmoid segment also showed ascending colon uptake. Another patient had ileal uptake with no colonic signal. The authors concluded that because PET demonstrated inflammatory activity in the colon despite negative endoscopic, histologic, and symptom assessment, this approach may contribute to an enhanced understanding of ulcerative colitis disease remission.

Inflammatory Bowel Diseases