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.

DIAGNOSIS

Autoantibodies and Chronic Heart Failure

In an article e-published on January 14 ahead of print in the *International Journal of Cardiology*, Aso et al. from the Shinshu University School of Medicine (Matsumuto, Japan) reported on a study using ^{123}I-MIBG scintigraphy to investigate the relationship between cardiac stimulation by anti-β-1-adrenoreceptor autoantibodies and myocardial sympathetic nerve activity in patients with chronic heart failure. The study included 52 patients who were screened for the autoantibodies. ^{123}I-MIBG scintigraphy was performed at 15 min and 3 h after tracer injection in 27 of the patients. The researchers found that patients with New York Heart Association functional class III or IV had higher levels of anti-β-1-adrenoreceptor autoantibodies than those with class I or II and that the autoantibody level was significantly correlated with heart-to-mediastinum radioactivity ratio and washout rate. Those patients who had experienced a cardiac event showed higher levels of autoantibodies, and cardiac event–free survival was lower in patients with autoantibody levels >10 U/mL. The authors concluded that "anti-β-1-adrenoreceptor autoantibodies are closely associated with cardiac sympathetic nervous activity assessed by ^{123}I-MIBG and cardiac event in patients with chronic heart failure."

International Journal of Cardiology

PET and Renovascular Disease

In an article e-published on January 2 ahead of print in *Hypertension*, Xia et al. from the Johns Hopkins Medical Institutions (Baltimore, MD) and the Mayo Clinic College of Medicine (Rochester, MN) reported on in vivo PET imaging and in vitro quantitative autoradiography of the angiotensin II subtype 1 receptor (AT1R) in a swine model of renovascular hypertension. The study included 24 pigs (11 controls; 13 with hemodynamically significant renal artery stenosis, 4 of which had been treated with lisinopril for 2 wk before imaging) that underwent ^{11}C-KR31173 PET. The researchers found that radioligand retention was significantly higher in hypoperfused kidneys of untreated and lisinopril-treated pigs than in those of controls. Increased tracer binding on PET was confirmed by in vitro autoradiography. Results from both in vivo and in vitro binding assessments indicated that lisinopril treatment did not eliminate the effect of renal artery stenosis on the AT1R. The authors concluded that these "findings support the concept of introducing AT1R PET as a diagnostic biomarker of renovascular disease."

Hypertension

Systolic Dysfunction in Renal Transplantation

Siedlecki et al. from Washington University (St. Louis, MO) and the University of Alabama (Birmingham) reported in the December 27 issue of *Transplantation* (2007;84:1610–1617) on a study using SPECT to assess the effect of left ventricular systolic dysfunction on survival after renal transplantation. The study included 653 renal transplant recipients who underwent stress myocardial perfusion SPECT imaging before the transplant procedure. Of these, 119 (18%) were found to have left ventricular (LV) systolic dysfunction. This group of patients had higher proportions of males, smokers, LV hypertrophy, previous left heart catheterization, and longer exposure to dialysis than those with normal LV ejection fraction. Over an approximately 3-y follow-up, 66 patients died and 67 additional patients experienced at least 1 nonfatal cardiac-related event. Patients with LV systolic dysfunction were at significantly higher risk for cardiac events and experienced higher all-cause mortality over the follow-up period. LV systolic dysfunction was associated with a 5-fold increase in cardiac mortality risk, a 2-fold increase in all-cause mortality, and a 70% increase in posttransplant cardiac complications. The authors concluded that "systolic dysfunction is associated with increased risk for overall and cardiac-related death and nonfatal events after renal transplantation, an association independent of ischemic disease."

Transplantation

Anesthetic Effect of Xenon

Salmi et al. from the Turku PET Center (Finland) reported in the January issue of *Anesthesia and Analgesia* (2008;106:129–134) on a study using ^{11}C-flumazenil PET to study the effect of xenon on γ-aminobutyric acid type A (GABA[A]) receptors in

an effort to elucidate the mechanism of xenon's anesthetic effects in the living human brain. The study included 8 healthy men who underwent 2 PET studies, 1 awake and 1 at approximately 1 minimum alveolar concentration of xenon (65%).The researchers found no significant changes in heart rate or mean arterial blood pressures in the imaging sets, and xenon was not found to significantly affect tracer binding in any brain region. The authors concluded that, despite reports in the literature on effects exerted by xenon on GABA(A) receptors, results from this study suggest that the "anesthetic effect of xenon is not mediated via the GABA(A) receptor system."

Anesthesia and Analgesia

Age, rCBF, and Thirst

Farrell et al. from the University of Melbourne (Parkville, Australia) reported in the January issue of the *Proceedings of the National Academy of Sciences USA* (2008;105:382–387) on a PET study assessing age-related changes in brain responses to thirst and drinking in healthy men. The study included 10 younger men (mean ages, 23.7 ± 2.8 y) and 12 older men (mean ages, 68.1 ± 3.4 y) in whom thirst was induced with hypertonic infusions. Each participant underwent $H_2{}^{15}O$ PET imaging before, during, and after thirst induction, and blood samples were collected at 5 stages during imaging. Participants rated changes in thirst on a scale, and these ratings were correlated with average regional cerebral blood flow (rCBF) findings on PET. The effects of drinking water were assessed by correlating the volume of intake with changes in rCBF from the point of maximum thirst to after-drinking imaging. Older participants drank less water than their younger counterparts in the study. Although thirst-related activation was seen in the primary sensorimotor cortex, prefrontal cortex, anterior midcingulate cortex, premotor cortex, and superior temporal gyrus in both groups, the researchers found a greater reduction in anterior midcingulate cortex rCBF relative to water intake in the older group. The authors summarized their findings: "Aging is associated with changes in satiation that militate against adequate hydration in response to hyperosmolarity, although it is unclear whether these alterations are due to changes in primary afferent inflow or higher cortical functioning."

Proceedings of the National Academy of Sciences USA

PET and Effects of Food Restriction

Thanos et al. from the Brookhaven National Laboratory (Upton, NY) reported in the January issue of *Synapse* (2008;62:50–61) on a PET study assessing the effects of food restriction on dopamine D_2 receptors in a genetic rodent model of obesity characterized by leptin-receptor deficiency. The researchers compared dopamine D_2 receptor levels in Zucker obese and lean rats at 1 and 4 mo of age and with restricted and unrestricted food access using both in vivo ^{11}C-raclopride microPET and in vitro ^{3}H-spiperone autoradiography. Both types of imaging showed dopamine receptors to be higher at 1 mo than at 4 mo in all animals and that food-restricted animals had higher dopamine D_2 receptor levels than those with unrestricted intake. Significant differences were seen in the results of the 2 imaging techniques at 4 mo. Autoradiography indicated that at 1 mo and 4 mo, unrestricted lean rats had significantly higher dopamine receptor binding than obese unrestricted rats but indicated no differences between restricted obese and restricted lean rats. Autoradiography also indicated that declines in dopamine D_2 receptors between 1 and 4 mo were significantly attenuated in both obese and lean food-restricted rats. PET imaging, however, indicated that at 4 mo, obese unrestricted rats showed greater dopamine receptor availability than lean unrestricted rats. No differences between obese restricted and lean restricted rats were observed, as with autoradiography. The authors concluded that these results suggest that: (1) differences in dopamine activity and dopamine D_2 receptor levels between obese and lean Zucker rats were modulated by access to food and (2) autoradiographic findings on attenuation of the age-related loss of dopamine receptor binding corroborates previous studies of the salutary effects of food restriction in aging. They also noted that "because ^{11}C-raclopride is sensitive to competition with endogenous dopamine, the higher dopamine D_2 receptor binding in obese rats with raclopride despite the lower dopamine D_2 receptor levels shown with spiperone could reflect lower extracellular dopamine in the obese rats and merits further investigation."

Synapse

β2-nAChR Availability in PTSD

In an article e-published on January 11 ahead of print in the *International Journal of Neuropsychopharmacology*, Czermak et al. from the Yale University School of Medicine (New Haven, CT) and the Veterans Affairs Connecticut Healthcare System (West Haven) reported on a study of nicotinic acetylcholine receptors containing β2 subunits (β2-nAChRs) in symptomatic patients with posttraumatic stress disorder (PTSD). The study included never-smoking PTSD patients, never-smoking healthy volunteers, and a subgroup of participants with a history of smoking. ^{123}I-5-IA-85380 SPECT was used to assess the availability of β2-nAChRs in the mesiotemporal cortex, prefrontal cortex, thalamus, and striatum. Severity of PTSD symptoms was assessed using the Clinician-Administered PTSD Scale. Never-smoking PTSD patients showed significantly higher tracer binding in the mesiotemporal cortex than never-smoking healthy controls. PTSD patients showed a significant correlation between the "reexperiencing" symptom cluster and thalamic tracer binding. The authors concluded that these find-

ings "not only suggest an involvement of β2-nAChRs in the pathophysiology of PTSD but also raise the possibility that this receptor may be a novel molecular target for drug development."

International Journal of Neuropsychopharmacology

PET in Cholangiocarcinoma

Kim et al. from the University of Ulsan College of Medicine (Seoul, Korea) reported on January 2 ahead of print in the *American Journal of Gastroenterology* on a study comparing the clinical roles of ^{18}F-FDG PET/CT and conventional imaging in patients with suspected and potentially operable cholangiocarcinoma. The study included 123 patients with suspected cholangiocarcinoma who had previously undergone biliary dynamic CT and MR imaging/MR cholangiopancreatography with MR angiography. Patients with overt unresectable cholangiocarcinoma or gallbladder cancer on conventional imaging were not included in the study. All patients underwent PET/CT imaging. Overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET/CT in primary tumor detection were 84.0%, 79.3%, 92.9%, 60.5%, and 82.9%, respectively, with no significant advantage over CT or MR imaging in the diagnosis of primary tumor. However, PET/CT showed significantly higher accuracy than CT in the diagnosis of regional lymph nodes metastases (75.9% and 60.9%, respectively) and distant metastases (88.3% and 78.7%, respectively). Assessment of resectability was also enhanced by PET/CT when compared with the results from conventional imaging. The authors concluded that PET/CT "improved the accuracy of preoperative staging in patients with cholangiocarcinoma planning to undergo curative resection" and thus had "an important clinical impact on the selection of proper treatment."

American Journal of Gastroenterology

PET in Pancreatic Cancer Surgery

Wakabayashi et al. from Kagawa University (Japan) reported in the January 7 issue of the *World Journal of Gastroenterology* (2008;14:64–69) on a study evaluating the role ^{18}F-FDG PET in the surgical management of patients with pancreatic cancer, including diagnosis, staging, and selection of patients for surgery. The study included 53 patients with primary pancreatic cancer, each of whom underwent PET and CT imaging, cytological examination of bile or pancreatic fluids, and assessment of serum levels of carcinoembrionic antigens (CEA) and carbohydrate antigen 19-9 (CA19-9). The sensitivity of PET, CT, cytological examination, and serum levels of CEA and CA19-9 were 92.5%, 88.7%, 46.4%, 37.7%, and 69.8%, respectively. PET was superior to CT only in diagnosing distant disease (bone metastases), whereas for local staging, the sensitivity of CT was better than that of PET. Standard uptake values (SUVs) on PET did not correlate with TNM stage or grade, invasiveness to vessels or nerves, or tumor size. However, a statistically significant difference was noted in SUVs in patients with resectable and unresectable disease. The authors concluded that although ^{18}F-FDG PET is useful in the diagnosis of pancreatic cancer, it is not sufficiently accurate for staging the disease. They added that "although the SUV does not correlate with the pathohistological prognostic factors, it may be useful in selecting patients who should undergo subsequent surgical treatment."

World Journal of Gastroenterology

Primary Tumor SUV and NSCLC

In the January issue of the *Journal of Thoracic Oncology* (2008;3:6–12), Berghmans and members of the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer reported on a metaanalysis of the literature conducted to derive a consensus view of the prognostic value of primary tumor standardized uptake values (SUVs) in non–small cell lung cancer (NSCLC). Thirteen eligible studies (total of 1,474 patients) were identified with the information required to perform the target analysis, which involved extracting estimates of the hazard ratio (HR) for comparing patients with low and high SUVs. Using data from these studies, the researchers aggregated individual HRs into a combined HR using a random-effects model. Eleven of the studies identified a high SUV as a prognostic factor for shorter survival, and 2 studies found no significant correlation between SUV and survival. The combined HR for the 13 reports was 2.27. The authors concluded that these results suggest "that the primary tumor SUV measurement has a prognostic value in NSCLC" and that these results should be confirmed in a metaanalysis focusing on individual patients' data.

Journal of Thoracic Oncology

THERAPY

RIT/Chemotherapy in NHL

In an article e-published on January 11 ahead of print in *Cancer*, Zinzani et al. from the University of Bologna (Italy) reported on the results of a prospective, single-arm, open-label, nonrandomized phase 2 trial of combined fludarabine and mitoxantrone chemotherapy plus radioimmunotherapy (RIT) in patients with untreated nonfollicular non-Hodgkin's lymphoma (NHL). The study included 26 patients with previously untreated, indolent, nonfollicular NHL (10 marginal zone lymphomas, 8 lymphoplasmacytic lymphomas, 8 small lymphocytic lymphomas) with 6 cycles of fludarabine and mitoxantrone chemotherapy followed 6–10 weeks later by ^{90}Y-ibritumomab tiuxetan. After chemotherapy, the overall response rate was 80.5%, including complete remission in 13 patients (50%) and partial remission in 8 patients (30.5%). Criteria for proceeding to RIT included at

least a partial remission with normal platelet counts and bone marrow infiltration <25%. Twenty patients (13 with complete and 7 with partial remissions) met these criteria and underwent RIT. Of these 20, 100% were in complete remission at the end of the treatment period. At a median follow-up of 20 months, the estimated 3-year progression-free survival rate was 89.5% and the estimated 3-year overall survival rate was 100%. ^{90}Y-ibritumomab tiuxetan toxicities included hematologic toxicities in 16 of 20 patients (neutropenia and thrombocytopenia). Five patients received transfusions of erythrocytes and/or platelets. The authors concluded that the positive results from this study provide support for "the feasibility, tolerability, and efficacy of the fludarabine and mitoxantrone plus ^{90}Y-ibritumomab tiuxetan regimen for the treatment of patients with untreated, indolent, nonfollicular NHL."

Cancer

MOLECULAR IMAGING

MR Imaging of $\alpha_v\beta_3$ Integrin Expression in Plaques

Burtea et al. from the University of Mons-Hainaut (Belgium) reported on January 10 ahead of print in *Cardiovascular Research* on a study assessing MR imaging of plaque-associated $\alpha_v\beta_3$ integrin expression in transgenic ApoE mice with a low-molecular-weight peptidomimetic of Arg-Gly-Asp grafted to gadolinium diethylenetriaminepentaacetate (Gd-DTPA-g-mimRGD). The results and evidence of specific molecular targeting were confirmed by use of the analogous compound Eu-DTPA-g-mimRGD and immunohistochemistry. Gd-DTPA-g-mimRGD was found to produce strong enhancement of external structures of the aortic wall and of deeper layers (tunica media and intima). Preinjection of Eu-DTPA-g-mimRGD diminished Gd-DTPA-g-mimRGD binding to atherosclerotic plaque and confirmed specific molecular targeting. The authors concluded that the new compound is "potentially useful for the diagnosis of vulnerable atherosclerotic plaques and of other pathologies characterized by $\alpha_v\beta_3$ integrin expression, such as cancer and inflammation." They cited the compound's delayed blood clearance, significant enhancement of signal-to-noise ratio, and the low immunogenicity of the mimetic molecule as promising aspects for applications in drug development and clinical use.

Cardiovascular Research

Tracking Monocytes in Atherosclerotic Lesions

In an article e-published on January 2 ahead of print in *Circulation*, Kircher et al. from the Massachusetts General Hospital, Harvard Medical School, and Brigham and Women's Hospital (Boston, MA) reported on the development of a noninvasive technique for in vivo imaging of monocyte trafficking to atherosclerotic lesions. The researchers used ^{111}In-oxyquinoline SPECT to visualize modulatory effects on monocyte recruitment to atherosclerotic lesions in live animals. They found that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors rapidly and substantially reduced monocyte recruitment to existing atherosclerotic lesions. The authors concluded that "this novel approach to track monocytes to atherosclerotic plaques in vivo should have broad applications and create new insights into the pathogenesis of atherosclerosis and other inflammatory diseases."

Circulation

Ultrasound and Antiangiogenic Therapy

Palmowski et al. from the German Cancer Research Center (Heidelberg) reported in the January issue of *Molecular Cancer Therapy* (2008;7:101–109) on a targeted ultrasound assessment of the early effects of antiangiogenic therapy. The researchers generated cyanoacrylate microbubbles linked to vascular endothelial growth factor receptor 2 (VEGFR2) and $\alpha_v\beta_3$ integrin–binding ligands and used quantitative volumetric ultrasound scanning to quantify their accumulation in squamous cell carcinoma xenografts. Imaging revealed the specificity of VEGFR2 and $\alpha_v\beta_3$ integrin–binding microbubbles. Targeted microbubbles accumulated in tumors at significantly higher rates than did nontargeted microbubbles. In addition, multimarker imaging could be performed during the same imaging session. Imaging also indicated a significant increase of VEGFR2 and $\alpha_v\beta_3$ integrin expression during tumor growth and a considerable decrease in both marker densities after matrix metalloproteinase inhibitor treatment. On the basis of these results and histologic data, the authors concluded that "targeted ultrasound appears feasible for the longitudinal molecular profiling of tumor angiogenesis and for the sensitive assessment of therapy effects in vivo."

Molecular Cancer Therapy

SPECT/CT in Cardiac Transplantation

Rao and colleagues from the Mayo Clinic (Rochester, MN) and the University of Pavia (Italy) reported in the December 27 issue of *Transplantation* (2007;84:1552–1666) on the feasibility of SPECT/CT imaging and quantification of cardiac gene expression after sodium iodide symporter (hNIS) gene transfer in cardiac transplantation. Donor hearts were perfused ex vivo with adenovirus-expressing hNIS (Ad-hNIS), Ad-Null, or University of Wisconsin (UW) solution prior to heterotopic transplantation into syngeneic rat recipients.The study focused on (1) perfused ex vivo rat hearts removed 5 days after transplantation and (2) a group of recipient rats that were imaged after injection of iodine on days 2–14 after transplantation. Higher ex vivo radioiodine counts were noted in the hearts perfused with Ad-hNIS than in either the UW or Ad-Null group. Image intensity in the Ad-NIS group was also significantly higher than in the UW or Ad-Null group. Sequential imaging of Ad-NIS–perfused hearts

between postoperative days 2 and 14 showed peak image intensity at day 5. Image intensities correlated well with ex vivo counts of radioactivity. The authors concluded that "these data demonstrate that hNIS gene transfer permits sequential real-time detection and quantification of reporter gene expression in the transplanted heart with micro-SPECT/CT imaging."

Transplantation

Molecular Scintigraphy of Neuroendocrine Tumors

In an article e-published on January 14 ahead of print in *Neuroendocrinology*, Binderup et al. from the University of Copenhagen (Denmark) reported on a study designed to quantify gene expression underlying the results of somatostatin receptor (sst) scintigraphy with ^{111}In-DTPA-octreotide and noradrenaline transporter (NAT) scintigraphy with ^{123}I-MIBG in patients with neuroendocrine tumors. Gene expression of somatostatin receptors 1–5 and NAT was measured by real-time polymerase chain reaction in 14 patients with neuroendocrine tumors and compared with similar metrics from 15 patients with colorectal adenocarcinomas. Scintigraphic results (9 ^{111}In-DTPA-octreotide and 3 ^{123}I-MIBG) were compared with gene expression results. The sst_2 was found to be upregulated in 13 of 14 patients (93%) with neuroendocrine tumors, and the absolute level of gene expression was highest for sst_2. Gene expression alterations of NAT and other sst subtypes were more variable. Positive octreotide scintigraphy correlated well with gene expression of sst_2. In 2 of 3 patients in whom ^{123}I-MIBG scintigraphy was positive, NAT was also upregulated. The sst_2 was generally downregulated in the colorectal tumor group, and gene expression of other receptors was more variable. The authors concluded that these results suggest that sst_2 is the best target for visualization of neuroendocrine tumors and that NAT is a useful target only in a subpopulation of these tumors. They added that, "comparison of scintigraphic results with quantitative gene expression may be used to achieve a better understanding of the link between them, which in turn could aid in planning and development of noninvasive molecular imaging of key molecular processes."

Neuroendocrinology