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

SPECT V/Q Scintigraphy Vs CTPA for PE

Miles and colleagues from a consortium of Australian research centers and hospitals reported on June 12 ahead of print in *Chest* on a comparison of SPECT lung scintigraphy and multislice CT pulmonary angiography (CTPA) in detection of pulmonary embolisms. The initial study group included 100 patients (≥50 y old) in whom pulmonary embolism was suspected. Of these, 79 underwent both diagnostic 16-detector CTPA and planar and SPECT ventilation/perfusion (V/Q) scintigraphy, and the results were compared. The sensitivity and specificity of SPECT scintigraphy alone were compared with diagnoses made by a panel of imaging specialists assessing CTPA and planar V/Q scintigraphy reports, clinical information, and 3-mo follow-up results. SPECT and CTPA were found to have a 95% agreement in diagnosis of pulmonary embolism. SPECT V/Q scintigraphy was determined to have a sensitivity of 83% and a specificity of 98%. The authors concluded that "this study indicates that SPECT V/Q scintigraphy is a viable alternative to CTPA for the diagnosis of pulmonary embolism and has potential advantages in that it was feasible in more patients, had fewer contraindications, lower radiation dose, and, arguably, fewer nondiagnostic findings compared to CTPA."

Chest

PET in Acupuncture Effectiveness Assessment

In an article e-published on June 6 ahead of print in *Neuroimage*, Harris et al. from the University of Michigan (Ann Arbor) reported on the use of PET to determine the effects and mechanisms of traditional Chinese acupuncture analgesia procedures on mu opioid receptors in the human brain. The researchers focused specifically on the possibility of elucidating mechanisms that could explain similar results in pain relief observed in traditional acupuncture, nontraditional acupuncture, and sham procedures in clinical trials. The study included a group of patients who were randomly assigned to receive either traditional Chinese acupuncture or sham acupuncture treatment over 4 wk. Each patient underwent ^{11}C-carfentanil PET imaging during the first treatment session and after the final (8th) treatment to assess mu opioid receptor binding. Traditional acupuncture resulted in short-term increases in mu opioid receptor binding potential in multiple regions (including the cingulate, insula, caudate, thalamus, and amygdala) as well as long-term increases in mu opioid receptor binding in several of the same structures (including the cingulate, caudate, and amygdala). These long-term effects were associated with greater reductions in clinically reported pain. Neither short- nor long-term effects were seen in patients undergoing sham treatment; in fact, over the course of the study, small reductions in mu opioid receptor binding were observed in these patients. The authors concluded that "these findings suggest that divergent mu opioid receptor processes may mediate clinically relevant analgesic effects for acupuncture and sham acupuncture."

Neuroimage

THC and Dopamine Release

Stokes et al. from the Imperial College/Hammersmith Hospital (London, UK) reported on June 16 ahead of print in *Neuroimage* on a study to determine whether recreational use of Δ9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis, increases dopamine release in the human striatum. A number of studies in recent years have associated cannabis exposure with an increased risk of psychosis, and several have suggested deregulation of dopaminergic systems as an underlying mechanism, particularly in adolescents. This study included 13 healthy volunteers with previous recreational cannabis exposure, who underwent ^{11}C-raclopride PET imaging, once after administration of 10 mg of THC and once after administration of a placebo. Each participant also was assessed with the Psychotomimetic States Inventory, a recently introduced instrument designed to measure the nature and extent of the phenomenologic effects of psychotropic drugs in schizophrenia-related research. THC was found to significantly increase psychosis-like symptoms as measured in this study by this test, but no corresponding increased effects of THC on ^{11}C-raclopride binding were seen on PET. The authors concluded that because "recreational cannabis users do not release significant amounts of dopamine from an oral THC dose equivalent to a standard cannabis cigarette," current models

of striatal dopamine release as the mechanism mediating cannabis as a risk factor for schizophrenia are challenged.

Neuroimage

Endogenous Endothelin, Myocardial Blood Flow, and Human Obesity

In an article e-published on June 18 ahead of print in *Obesity (Silver Spring)*, Mather et al. from the Indiana University School of Medicine (Indianapolis) reported on a study using PET imaging to assess the contribution of endogenous endothelin to the regulation of myocardial perfusion and vascular tone. The authors hypothesized that this contribution would be augmented in human obesity. The study included 10 lean and 9 obese individuals, all without hypertension, hyperlipidemia, or diabetes mellitus. All participants underwent NH_3-ammonia PET assessment of myocardial perfusion under resting and adenosine stress on 2 separate d, with and without concurrent exposure to BQ123, an antagonist of type A endothelin receptors. BQ123 exposure induced an increase in resting myocardial perfusion of ~40%, a percentage that was not significantly different in the lean and obese individuals. Body mass index and cholesterol levels, however, were significantly related to BQ123-induced increases in basal tone in multivariate analysis. No baseline differences were noted in adenosine-stimulated increase in blood flow between lean and obese subjects, with no BQ123 effects in either group. The authors concluded that "these observations suggest that endothelin is an important contributor to the regulation of myocardial perfusion under resting conditions in healthy lean and obese humans, with increased contributions in proportion to increasing obesity."

Obesity (Silver Spring)

Prognostic Value of Absence of Coronary Artery Calcification

Sarwar et al. from the Massachusetts General Hospital and Harvard Medical School (Boston) reported in the June issue of *JACC Cardiovascular Imaging* (2009;2:675–688) on a study using PET to assess the diagnostic and prognostic value of the absence of coronary artery calcification in asymptomatic and symptomatic individuals. The meta-analytic review of the literature included a search of 49 original research studies published in English between 1990 and 2008 examining the diagnostic and prognostic significance of coronary artery calcification. Of these, 13 studies assessed the relationship between calcification and adverse cardiovascular outcomes in 64,873 asymptomatic patients. In this group of asymptomatic individuals, 146 (0.56%) of the 25,903 without calcification were found to have had a cardiovascular event during a mean follow-up of 51 mo. Seven of the studies assessed the prognostic value of coronary artery calcification in a symptomatic population, among whom 1.80% without calcification proceeded to a cardiovascular event. Pooled results from 18 studies indicated that the presence of any calcification yielded a sensitivity and negative predictive value of 98% and 93%, respectively, for detection of significant coronary artery disease on conventional coronary angiography. Of 4,870 individuals undergoing myocardial perfusion imaging, only 6% of those with no calcification showed any signs of ischemia. The pooled results of 3 studies indicated that the absence of calcification had a negative predictive value of 99% for ruling out acute coronary syndrome. The authors concluded that on the basis of the review of these studies with a total of more than 85,000 patients, "the absence of coronary artery calcification is associated with a very low risk of future cardiovascular events, with modest incremental value of other diagnostic tests in this very low-risk group."

JACC Cardiovascular Imaging

Integrin $\alpha_v\beta_6$ Imaging in a Pancreatic Tumor Model

Hausner and colleagues from the University of California–Davis, the University of California–Santa Barbara, and the Barts and London Medical School (UK) reported on June 23 ahead of print in *Cancer Research* on targeted integrin $\alpha_v\beta_6$ imaging with an improved PET radiotracer in a model of pancreatic cancer. Several studies have suggested $\alpha_v\beta_6$ as a prognostic biomarker associated with poor survival. Hausner et al. expanded on their previous studies showing the feasibility of $\alpha_v\beta_6$ PET imaging with the peptide ^{18}F-FBA-A20FMDV2 by assessing improved imaging agents and proof-of-efficacy studies in a mouse model of endogenous $\alpha_v\beta_6$ expression. The most promising of the new agents, ^{18}F-FBA-PEG28-A20FMDV2, resulted in improved PET imaging in a mouse model with either a melanoma cell line (transduced $\alpha_v\beta_6$ expression) or the BxPC-3 human pancreatic carcinoma cell line (endogenous $\alpha_v\beta_6$ expression). Improved imaging was accompanied by enhanced tumor retention and good clearance of nonspecifically bound activity. The novel tracer was markedly superior to ^{18}F-FDG in PET imaging of BxPC-3 tumors. The authors concluded that the fact that pancreatic ductal adenocarcinoma tumors express $\alpha_v\beta_6$ "suggests that this probe has significant potential for the in vivo detection of this malignancy, thus having important implications for patient care and therapy."

Cancer Research

PET/CT-Guided Surgery in Relapsed Prostate Cancer

Winter et al. from the Klinikum Oldenburg (Germany) reported on June 16 ahead of print in *Aktuelle Urologie* on results of the use of ^{11}C-choline PET/CT–guided secondary lymph node surgery in patients with prostate-specific antigen (PSA) increases after radical prostatectomy. The study included 8 men with PSA relapses after radical prostatectomy and lymphadenectomy who underwent ^{11}C-choline PET/CT and were diagnosed with lymph node metastasis. Using data from PET/CT, lymph nodes that were suspected of metastasis and nearby

lymph nodes were openly dissected. Histology and PET/CT results were compared and then assessed against follow-up PSA assessments. Of 11 lymph nodes suspected of metastasis, 9 were confirmed at histologic analysis. All 12 of the nearby lymph nodes were correctly assessed as negative. On follow-up, 6 of 7 patients with histologic metastasis confirmation showed a PSA response, and 3 of the 6 patients with a single metastasis had complete PSA remissions without adjuvant therapy at a maximum follow-up of more than 2 y. The authors concluded that although these results suggest that ^{11}C-choline PET/CT can detect lymph node metastasis with high specificity and that this targeted surgical approach is promising, a larger longitudinal study is needed to provide conclusive data.

Aktuelle Urologie

PET in Full-Thickness Chest Wall Resections

Petermann et al. from the Centre Hospitalier Universitaire Vaudois (Lausanne, Switzerland) reported on June 10 ahead of print in *Interactive Cardiovascular and Thoracic Surgery* on the role of ^{18}F-FDG PET in preoperative planning for resection of full-thickness chest wall malignancies, a setting in which CT is currently most often used. The retrospective study included 18 patients in whom tumor extent was measured by both CT and PET, using the 2 largest perpendicular tumor extensions in the chest wall plane to compute tumor surface, assuming an elliptical shape. These results from imaging were compared with measures of tumor borders at histopathologic analysis. The authors found that CT consistently overestimated tumor size and that PET was significantly better at defining the size of lesions >24 cm^2, which corresponded to a mean diameter of >5.5 cm or an ellipse of $>4 \times 7.6$ cm. The authors concluded that, although "PET can complement CT in planning full-thickness chest wall resection for malignancies," its true value remains to be explored in larger clinical studies

Interactive Cardiovascular and Thoracic Surgery

PET/CT in Management of Anterior Mediastinal Masses

In an article e-published on June 4 in the *European Journal of Cardiothoracic Surgery*, Luzzi et al. from the Croce e Carle Hospital (Cuneo, Italy) reported on a study of the utility of ^{18}F-FDG PET/CT in preoperative assessment of isolated anterior mediastinal lesions, with a focus on decision support for biopsy vs. resection in surgical planning. The study included 19 patients (10 men, 9 women) who underwent PET/CT imaging as part of preoperative assessment for isolated anterior mediastinal disease. CT data, postoperative histology, and Masaoka staging of extent of disease for thymomas were compared with maximum standardized uptake values (SUVs) on PET/CT. Thymomas were divided into low- and high-risk types. The results of all studies showed 13 thymomas (6 low- and 7 high-risk), 3 lymphomas, and 3 other primitive thymic tumors (1 paraganglioma, 2 nonseminomatous germ cell tumors). The mean SUV in low-risk thymomas was significantly lower than in high-risk thymomas and in the lymphomas and other primitive anterior mediastinal tumors. Although a significant correlation was found between Masaoka stage and SUV in thymomas, no such correlation was found between SUV and tumor diameters as assessed on CT. The authors concluded that this experience suggests that "low SUV (<5) is associated with low-risk and minimally invasive thymoma (Masaoka stages I–II)" and therefore appropriate for direct resection. They added that "for lesions with an infiltrative aspect on CT scan associated with a higher SUV (>5), an open biopsy is mandatory to exclude mediastinal lymphomas or, in the case of high-risk thymoma, to address a neoadjuvant treatment."

European Journal of Cardiothoracic Surgery

PET and Skeletal Muscle Activity in Cycling

Gondoh et al. from the Tohoku University/National Institute of Fitness and Sports (Japan) reported on June 18 ahead of print in the *Journal of Applied Physiology* on a study of individual skeletal muscle activity during different intensities of pedaling exercises as determined by glucose uptake on ^{18}F-FDG PET imaging. The study included 20 healthy men (7 exercise participants and 13 control subjects). The exercise group underwent whole-body ^{18}F-FDG PET imaging after 35 min of cycle pedaling at 40% and 55% maximal oxygen consumption exercise intensities and again at rest. Mean ^{18}F-FDG uptake of the iliacus muscle and muscles of the anterior part of the thigh was significantly greater in the exercise group than in corresponding muscles in control subjects. At 55% maximal oxygen consumption in exercise, uptake in the iliacus muscle and thigh muscles, except for the rectus femoris, increased significantly compared with those at 40% maximal oxygen consumption. The authors stated that these results "are the first to clarify that, as well as the muscles of the anterior thigh, the iliacus muscle is the prime muscle used during pedaling exercise" and that "the iliacus muscle and all muscles in the thigh, except for the rectus femoris, contribute when the workload of the pedaling exercise increases from 40% to 55% maximal oxygen consumption."

Journal of Applied Physiology

THERAPY

RIT and a Disruptive Vascular Agent in GI Carcinoma

In an article e-published on June 23 ahead of print in *Clinical Cancer Research*, Meyer and colleagues from University College of London (UK) and a consortium of UK medical research centers reported on early results from a phase 1 trial of com-

bined radioimmunotherapy (RIT) with ^{131}I-A5B7 anti-carcinoembryonic antigen (CEA) antibody (^{131}I-A5B7) and a vascular disruptive agent, combretastatin-A4-phosphate (CA4P) in patients with gastrointestinal carcinomas. In 12 patients (mean age, 63 y; range, 32–77 y), the researchers conducted a phase 1 trial to determine dose-limiting toxicity and maximum tolerated dose as well as to assess the efficacy and mechanism of the combined treatment. The protocol included a starting dose of 1,800 MBq/m^2 of ^{131}I-A5B7 on d 1 with 45 mg/m^2 CA4P administered on d 3 and 4, a regimen that was repeated weekly up to 7 wk. At the first dose level, 2 patients experienced dose-limiting toxicities (grade 4 neutropenia), and 2 more experienced neutropenia at a reduced dose of 1,600 MBq/m^2. SPECT imaging confirmed tumor antibody uptake in all 10 assessable patients. At the end of the treatment period, 3 of these 10 had stable disease and 7 had progressive disease. Dynamic contrast-enhanced MR imaging confirmed falls in kinetic parameters in 9 of 12 patients during treatment. The authors concluded that although both RIT and the vascular disruptive agent were shown to function in this study, additional studies are needed to determine optimal dose and timing of both agents in order to enhance efficacy.

Clinical Cancer Research

Pretargeting RIT in Hematolymphoid Tissues

Green et al. from the Fred Hutchinson Cancer Research Center (Seattle, WA) reported on June 10 ahead of print in *Blood* on a study of the potential therapeutic advantage of pretargeted radioimmunotherapy (RIT) in 19 nonhuman primates. The authors compared the results of anti-CD45 pretargeted RIT with those of conventional RIT with a directly radiolabeled bivalent antibody.

Radiolabeled-DOTA-biotin administered 48 h after anti-CD45 streptavidin fusion protein resulted in significantly lower concentrations of radiation in nontarget tissues (higher target-to-normal ratios) than did conventional RIT, with higher retention in target tissues than seen in directly radiolabeled anti-CD45 RIT. The timing of RIT after pre-RIT significantly affected biodistribution. No synthetic clearing agent was needed for the fusion protein, which cleared rapidly from the circulation. The authors concluded that "these results support proceeding to anti-CD45 PRIT clinical trials for patients with both leukemia and lymphoma."

Blood

Novel Hybrid Peptide for Melanoma Therapy

Yang et al. from the University of New Mexico (Albuquerque) and the University of Missouri (Columbia) reported on June 24 ahead of print in *Bioconjugate Chemistry* on a study designed to determine whether arginine-glycine-aspartic (RGD)–conjugated α-melanocyte stimulating hormone (α-MSH) hybrid peptide can be used to target melanocortin-1 receptors for potential melanoma therapy and whether ^{99m}Tc SPECT/CT imaging could be used to effectively assess such therapy. The authors described the development of the peptide and initial binding affinity studies in vitro in B16/F1 melanoma cells and in melanoma-bearing C57 mice. The radioloabeled peptide showed excellent receptor binding affinity, with rapid cell internalization and extended retention. In vivo studies showed high tumor uptake at 2 h after injection and prolonged tumor retention with rapid whole-body clearance. SPECT/CT of the radiolabeled peptide clearly visualized melanoma tumors in mice. In in vitro studies, a single treatment of the peptide decreased the clonogenic survival of B16/F1 cells by 65% compared with results in untreated control cells. The authors concluded that the favorable melanoma targeting properties and remarkable cytotoxic effects of this novel hybrid peptide warrant additional studies.

Bioconjugate Chemistry

Amyloid-β Protein and Inhibition of Tumor Cell Proliferation

Zhao et al. from the Brigham and Women's Hospital and the Harvard Medical School (Boston, MA) reported in the June 1 issue of *Cancer Cell International* (2009;9:15) on a study designed to provide basic molecular data that might more fully inform the frequent observation that Alzheimer's disease and cancer do not occur simultaneously at rates that might be expected if their respective incidences and progressions were entirely independent. Using bioluminescent imaging of multiple tumor cell lines (human glioblastoma U87, human breast adenocarcinoma MDA-MB231, and mouse melanoma B16F) that stably express luciferase, the authors observed significant inhibition of cell proliferaition when exposed to a conditioning medium made from amyloid precursor protein–overexpressing cells. They concluded that these results suggest that amyloid β "plays an inhibitory role in tumor cell proliferation; this effect could depend on the type of tumor cells and amount of amyloid β."

Cancer Cell International

Reporter Gene Imaging of a Genetically Modified Vaccinia Virus

In the June 1 issue of *Clinical Cancer Research* (2009;15:3791–3801) Brader et al. from the Memorial Sloan–Kettering Cancer Center (New York, NY) reported on studies to determine whether a genetically modified vaccinia virus, GLV-1h99, containing a human norepinephrine transporter (hNET) reporter gene, could be sequentially monitored by ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) γ-camera imaging and ^{124}I-MIBG PET. In vitro studies included assessment of GLV-1h99 in human malignant mesothelioma and pancreatic cancer cell lines for cytotoxicity, expression of the hNET protein, and

tracer uptake in cell cultures, with peak uptake achieved at 48 h after virus infection. In vivo γ-camera and PET imaging was performed in mice with MSTO-211H orthotopic pleural mesothelioma tumors. The modified vaccinia virus successfully infected and provided dose-dependent levels of transgene hNET expression in human malignant mesothelioma and pancreatic cancer cells. In vivo hNET expression in tumors could be imaged by scintigraphy at 48 h and by PET at 72 h after virus administration. The authors concluded that these positive results reinforce the contention that "the inclusion of human reporter genes into recombinant oncolytic viruses enhances the potential for translation to clinical monitoring of oncolytic viral therapy."

Clinical Cancer Research

Real-Time, Multicolor Quantum Dot Lymphatic Imaging

Kosaka et al. from the group of prolific molecular imaging researchers at the Center for Cancer Research at the National Institutes of Health (Bethesda, MD) continued their reports on novel quantum dot advances with an article e-published on June 18 ahead of print in the *Journal of Investigative Dermatology.* They reported on a method of in vivo multicolor lymphatic imaging using cadmium–selenium quantum dots in a fluorescence imaging system that enabled simultaneous visualization of up to 5 distinct lymphatic basins in real time. The approach used 5 visually well-distinguishable carboxyl quantum dots that were injected subdermally into 7 mice at 5 different sites and serially imaged with real time multicolor lymphatic imaging either noninvasively or in situ during surgery. The resulting images successfully distinguished all 5 lymphatic basins with different colors in real time, with lymph node visualization lasting to at least 7 d. They concluded that "this method could have a considerable potential in lymphatic research for studying the anatomy and flow within the lymphatic system as well as in some limited clinical settings where real-time visible fluorescence could facilitate procedures under surgery or endoscopy."

Journal of Investigative Dermatology

PET in Peutz-Jeghers Syndrome

On June 18 ahead of print in the *Proceedings of the National Academy of Sciences USA,* Shackelford et al. from the Salk Institute for Biological Studies (La Jolla, CA) reported on PET studies of mechanisms of tumor metabolism in a mouse model of Peutz-Jeghers syndrome (PJS). PJS, also called hereditary intestinal polyposis syndrome, an autosomal dominant genetic disease characterized by the development of gastrointestinal (GI) hamartomas and a predisposition to development of malignancies both in the GI tract and elsewhere. The disease is associated with inherited loss of function mutations in the LKB1/STK11 serine/threonine kinase. In this study, the researchers showed that GI polyps in LKB1± mice and AMPK-deficient mouse embryonic fibroblasts demonstrate dramatic upregulation of the HIF-1α transcription factor and its downstream transcriptional targets. The HIF-1α targets hexokinase II and Glut1 are upregulated in these polyps. PET imaging of the mouse polyps showed increased glucose utilization in focal GI regions corresponding to these gastrointestinal hamartomas. In addition, polyps from Peutz-Jeghers patients similarly exhibited upregulated signaling, HIF-1α, and GLUT1 levels. They concluded that "these findings suggest a number of therapeutic modalities for the treatment and detection of hamartomas in PJS patients, and potential for the screening and treatment of the 30% of sporadic human lung cancers bearing LKB1 mutations."

Proceedings of the National Academy of Sciences USA