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. Note that although we have divided the articles into therapeutic and diagnostic categories, these lines are increasingly blurred as nuclear medicine capabilities rapidly expand. Many diagnostic capabilities are now enlisted in direct support of and, often, in real-time conjunction with, therapies. 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.

Therapy

Heidelberg Ion Therapy Center

Several review articles and press releases have described the ion beam therapy facility under construction at the Department of Clinical Radiology at the University of Heidelberg (Germany). The most complete set of scientific analyses and reports appeared in a December 2004 supplement to *Radiotherapy and Oncology*, the journal of the European Society for Therapeutic Radiology and Oncology. Haberer et al. (*Radiother Oncol.* 2004;73[suppl 2]:S186–S190) provided a general description of the Heidelberg Ion Therapy Center, which will be the first dedicated and hospital-based irradiation facility for protons and heavier ions in Europe. The center will include 2 horizontally fixed beamlines for patient treatment with protons and carbon ions and a fixed-beam experimental area, with a total capacity of more than 1,000 patient treatments each year and space for approximately 80 support staff members. Researchers will be able to use different ions under identical conditions to determine which particles are most suitable in specific treatment applications. A synchrotron will accelerate particles to energies corresponding to water-equivalent ranges from 2 to 30 cm. An intensity-controlled raster scanning technique will be used to optimize the use of the favorable depth dose for direct distribution of ions into tumor.

In a recent interview conducted by Siemens Medical Solutions, a main supplier of scientific and imaging apparatus to the project, Imtraut Gurkan, director of administration of the University Clinic Heidelberg, said, "With this step, we have met the important technical prerequisites that allow us to begin treating patients with tumors that up to now have been considered to be incurable. By using different particle therapies, a wider variety of tumor sites may be treated."

Commissioning of the facility's sections is scheduled to begin in 2006, with preclinical operation slated for 2007. Scientific, technical, and clinical prerequisites for the Heidelberg Ion Beam Therapy Center have been a joint project of the University Clinic Heidelberg, the German Cancer Research Center, the Gesellschaft für Schwerionenforschung (GSI), and the Research Center Rossendorf.

PET will be an essential element in the new center. Enghardt et al. (*Radiother Oncol.* 2004;73[suppl 2]: S96–S98) emphasized that PET imaging of the radioactivity distributions induced by therapeutic irradiation is currently the only feasible method for in situ and noninvasive monitoring of radiooncology treatments with ion beams. These authors described activities at GSI, where, in preparation for the opening of the Heidelberg center, researchers are investigating experimental carbon ion therapy and have developed an interactive approach for PET-guided quantification of local dose deviations as part of treatment planning. Other informative articles about review of clinical trials and preparation for treatment planning at the center include those by Jakel et al. (*Radiother Oncol.* 2004; 73[suppl 2]:S86–S91) and Schulz-Ertner et al. (*Radiother Oncol.* 2004; 73[suppl 2]:S53–S56).

Radiotherapy and Oncology

^{90}Y-mAb RIT Research in Ovarian Carcinoma

In an article e-published ahead of print on May 31 in *Cancer Immunology and Immunotherapy*, Coliva et al. from the Istituto Nazionale Tumore (Milan, Italy) reported on development of a ^{90}Y-labeled monoclonal antibody (mAb MOv18) and preclinical validation of a protocol for radioimmunotherapy of human ovarian carcinomas. The authors described the production of the labeled mAb in laboratory conditions and determined that the radiolabeled preparations were stable in human serum, with >97% radioactivity associated to mAb at 48 hours after labeling. They analyzed the abilities of both ^{90}Y- and ^{111}In-labeled MOv18 to localize folate receptors in nude mice bearing tumors induced by isogenic cell lines differing only in the presence or absence of the relevant antigen. Uptake in tumor areas was significantly higher than in nontumor areas and in mock tumor tissues, with uptake values for the ^{90}Y-labeled tracer higher than those for the ^{111}In-labeled tracer. They concluded that "these data demonstrate the feasibility of ^{90}Y-labeling of MOv18 without compromising antibody binding ability and the immunoreagent-specific localization in vivo on folate receptor–expressing tumors, suggesting the suitability of ^{90}Y-MOv18 for clinical studies."

Cancer Immunology and Immunotherapy

Intratumoral RIT in Glioblastoma

Boiardi et al. from the Istitutio Nazionale Neurologico (Milan, Italy) reported in the April issue of the *Journal of Neurooncology* (2005;72: 125–131) on the intratumoral delivery of mitoxantrone in association with ^{90}Y radioimmunotherapy (RIT) in recurrent glioblastoma. The study included 26 patients with recurrent glioblastoma who were enrolled for a second surgery to remove recurrent tumor and for placement of an Ommaya reservoir to allow local delivery of chemotherapy and direct pretargeted RIT. All patients underwent partial tumor resection, and residual masses were >2 cm in 75% of patients. After surgery, all patients underwent a second schedule of systemic chemotherapy and received 2 cycles of locally delivered ^{90}Y RIT within a 10-week period. Neurologic examinations were performed each month and MR or contrast-enhanced CT imaging was performed at 2-month intervals to assess responses. The progression-free survival for the patients was 61% at 6 months and 22% at 12 months. Survivals after recurrence at 6, 12, and 18 months were 80%, 53%, and 42%, respectively. No major side effects were noted from the RIT. The authors concluded by stressing that "the combined treatments could be more effective if delivered into a smaller residual tumor mass and probably in an adjuvant setting before tumor recurrence."

Journal of Neurooncology

Cytotoxicity of ^{111}In-Labeled Antibodies

In the June issue of *Molecular Cancer Therapy* (2005;4:927–937), Michel et al. from the Center for Molecular Medicine and Immunology (Belleville, NJ) reported on a study designed to assess the in vitro cytotoxicity of anti-HER-2 antibodies conjugated to ^{111}In or ^{125}I. Target cells in the study were the breast carcinoma SK-BR-3 and the ovarian carcinoma SK-OV-3.ip1. Antibody accumulation and catabolism during a 2–3-day incubation with antibody were measured to assure that uptake was sufficient to make cell killing feasible. Cells were incubated for 2 days with the labeled antibody, then assayed for colony-forming units with a limiting dilution assay to test for cytotoxicity. SK-BR-3 cells were strongly killed, and SK-OV-3.ip.1 cells were more resistant to killing. However, a 2-antibody mixture produced 100% killing in the breast carcinoma cells and somewhat enhanced killing in the ovarian carcinoma cells. ^{111}In-labeled antibodies to other high-density antigens, epithelial glycoprotein-1, and epithelial glycoprotein-2, also killed these target cells. Unlabeled antibodies produced much less cytotoxicity, and, although ^{131}I-labeled antibodies resulted in high levels of nonspecific cytotoxicity, they produced essentially no specific cytotoxicity.

Molecular Cancer Therapy

Diagnosis

2-^{11}C-Thymidine PET in Abdominal Malignancies

Wells et al. from the Imperial College of London (UK) reported in the June 15 issue of *Clinical Cancer Research* (2005;11:4341–4347) on a small group study designed to evaluate the reproducibility and reliability of 2-^{11}C-thymidine PET in patients with advanced intraabdominal malignancies. The study included 7 patients who were scanned twice, with 1-week interval and no intervening therapy. Interpatient and intrapatient variability of both blood and tissue data were assessed. The authors found interpatient variability in the levels of the tracer and its main metabolite, $^{11}CO_2$, in plasma. Variability in PET data was greater between patients than in repeated imaging of same patients. The authors stated that this is the first report showing that 2-^{11}C-thymidine PET scanning is reproducible in humans and that "repeat scanning of tumor proliferation using 2-^{11}C-thymidine PET is feasible to perform in human intraabdominal malignancies and should aid the future rapid assessment of antiproliferative tumor agents."

Clinical Cancer Research

Avascular Necrosis in Multiple Myeloma Treatment

In an article e-published ahead of print on June 13 in the *Journal of Clinical Oncology*, Talamo et al. from the University of Arkansas for Medical Sciences (Little Rock) reported on a study designed to assess the prevalence, time of onset, risk factors, and outcome of avascular necrosis (AVN) of bone in patients with multiple myeloma undergoing antineoplastic therapy. The study included the use of PET to assess abnormal uptake and included 553 patients who were enrolled in a treatment protocol consisting of dexamethasone-containing induction chemotherapy, autologous stem-cell transplantation, consolidation chemotherapy, and maintenance with interferon alfa. Patients were randomly assigned to receive thalidomide or no thalidomide during the study period. During a median follow-up of 33 months, AVN of the femoral head(s) developed in 49 patients (9%), with a median time to onset in these patients of 12 months. The 3 strongest risk factors for development of AVN were a higher total dexamethasone dose, male sex, and younger age. Thalidomide-treatment did not affect development of AVN. ^{18}F-FDG PET failed to detect any abnormal uptake in the AVN affected bones. The authors noted that although AVN is a rare and usually asymptomatic complication during myeloma, the risk factors should be considered.

Journal of Clinical Oncology

Brain Mu-Opioid Receptors in Cocaine Users

Gorelick et al. from the National Institute on Drug Abuse (Bethesda,

MD) and the Department of Health and Human Services (Baltimore, MD) reported in the June 15 issue of *Biological Psychology* (2005;57:1573–1582) on a study evaluating the time course of craving in cocaine users with PET imaging of brain mu-opioid receptors (mOR). Several of the authors had been part of a previously published Johns Hopkins–based study (*Nat Med.* 1996;2:1225–1229) using ^{11}C-carfentanil PET to show increased mOR binding in brain regions of 10 cocaine-dependent men after 1 and 28 days of abstinence. The current study included 17 cocaine users in whom regional brain mOR binding potential was measured with ^{11}C-carfentanil PET over 12 weeks of cocaine abstinence and 16 healthy control volunteers who underwent the same imaging. In the cocaine users, mOR binding potential was increased in the frontal, anterior cingulate, and lateral temporal cortex after 1 day of abstinence. Binding potential remained elevated in the anterior cingulate and anterior frontal cortex after 12 weeks. Increased binding in some regions at 1 day and 1 week was positively correlated with self-reported cocaine craving. mOR binding potential was significantly correlated with the percentage of days on which cocaine had been used during the 2 weeks before initiation of the study, the amount of cocaine used each day, and with urine benzoylecgonine concentration measured at the first PET scan. The authors concluded that these results "suggest that chronic cocaine use influences endogenous opioid systems in the human brain and might explain mechanisms of cocaine craving and reinforcement."

Biological Psychology

^{18}F-FDG PET Assessed in Insulitis and Prediabetes

In an article published ahead of print on June 10 in *Diabetes Research and Clinical Practice*, Kalliokoski et al. from the University of Turku and the Central Hospital of Seinajoki (Finland) reported on the results of an autoradiographic study of ^{18}F-FDG uptake in nonobese diabetic (NOD) mice, designed to gauge the potential utility ^{18}F-FDG PET in the assessment of insulitis and prediabetes in humans. The authors compared ^{18}F-FDG uptake in the pancreas and pancreatic islets of healthy BALB/c mice, phenotypically healthy NOD mice with insulitis, and diabetic NOD mice. Mice were killed 90 minutes after ^{18}F-FDG injection, and digital autoradiography was used to analyze distribution of radioactivity. No correlation was found between plasma glucose concentrations and tracer uptake values. In NOD mice, uptake to islets affected by insulitis was up to 2.3 times higher than that to unaffected islets in the same pancreas. Uptake to NOD islets with insulitis was also clearly greater than that in these islets in the BALB/c mice. The authors concluded, however, that because of the relatively small difference in intensity between uptake in healthy and diseased islets and the limited resolution of PET, that ^{18}F-FDG PET does not appear a promising approach to in vivo documentation of onset and progression of insulitis and prediabetes in mouse or humans.

Diabetes Research and Clinical Practice

Comparative Value of PET/CT in Posttherapy Staging of Esophageal Cancer

Cerfolio et al. from the University of Alabama at Birmingham reported in the June issue of the *Journal of Thoracic Cardiovascular Surgery* (2005;129:1232–1241) on a prospective study on the efficacies of various diagnostic procedures in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. The study included 48 patients with esophageal cancer who underwent initial chest, abdomen, and pelvis CT scans; endoscopic ultrasound with fine-needle aspiration (EUS/FNA), and ^{18}F-FDG PET/CT; neoadjuvant chemoradiotherapy; repeat staging tests; and pathologic staging in the 41 patients who underwent esophagogastrectomy with lymphadenectomy. The accuracy of the tests under analysis for distinguishing pathologic T4 from T1–T3 disease was 76% for CT, 80% for EUS/FNA, and 80% for PET/CT. The accuracy for identifying nodal disease was 78% for CT, 78% for EUS/FNA, and 93% for PET/CT. PET/CT was true-positive in identifying M1b disease in 4 patients, false-positive in 4 patients, and false-negative in 2 patients, whereas for CT these numbers were 3, 3, and 3 patients. PET/CT accurately predicted complete response in 89% of the 15 patients who were complete responders, compared with only 67% for EUS/FNA and 71% for CT. The authors concluded that ^{18}F-FDG PET/CT is more accurate than either EUS/FNA or CT scan for predicting nodal status and complete responders after neoadjuvant therapy for esophageal cancer. They added, however, that although PET/CT and CT provide targets for biopsy, the results are often false-positive.

Journal of Thoracic Cardiovascular Surgery

^{18}F-FDG PET in Cartilage Neoplasms

In the July issue of *Skeletal Radiology* (2005;34:367–374), Feldman et al. of the New York Presbyterian Medical Center (NY) reported on the value of ^{18}F-FDG PET in defining aggressive cartilage neoplasms, focusing on those with problematic or borderline histologic, imaging, and clinical characteristics. The study included 20 females and 9 males (ages 11–85 years) with cartilage lesions who underwent whole-body ^{18}F-FDG PET imaging. A statistically significant maximum standardized uptake value cutoff of 2.0 was used to distinguish benign from malignant cartilage neoplasms, and these values were then correlated with histopathologic findings in the 26 patients who underwent surgery. The overall sensitivity of whole-body ^{18}F-FDG PET in distinguishing benign and malignant lesions was 90.9%, specificity

was 100%, and accuracy was 96.6%. The authors concluded that PET "is a valuable adjunct in identifying primary, recurrent, and metastatic cartilage malignancies" and that the functional data supplied may facilitate individually tailored treatment management and decision making.

Skeletal Radiology

^{18}F-PET Thyroid Incidentaloma

In the June issue of *Laryngoscope* (2005;115:1074–1078), Kim et al. from the University of Ulsan College of Medicine (Seoul, Korea) reported on a retrospective study of incidental thyroid ^{18}F-FDG uptake in PET evaluation of cancer patients and on the role of standard uptake value (SUV) measurement in differentiation of thyroid malignancy from benign disease. The study included the records of 4,136 individuals who had undergone ^{18}F-FDG PET imaging for evaluation of known malignancies not associated with the thyroid. Maximum SUVs of identified thyroid lesions were recorded, and fine-needle aspiration results were reviewed. Out of the total number of patients imaged, 94 (2.2%) were found to have focal (1.1%) or diffuse (1.1%) thyroid tracer uptake, with a higher incidence of both focal and diffuse uptake in women than in men. Cytologic results were available in 32 of the 45 individuals with focal thyroid uptakes. In 16 of these patients, the tumor was found to be malignant (14 papillary thyroid carcinomas and 2 metastases from breast and esophageal cancers). The remaining 16 were cytologically diagnosed with follicular cell lesions (follicular neoplasm, nodular hyperplasia, or indeterminate follicular lesion). No significant differences were noted between maximum SUV in benign and malignant thyroid nodules. In the 45 patients with diffuse thyroid uptake, presumptive diagnosis of chronic thyroiditis was possible in 34 patients by clinical and laboratory findings. The authors concluded that these data suggested that "a cytologic diagnosis of focal thyroid ^{18}F-FDG PET incidentaloma regardless of SUV is mandatory considering the very high prevalence of thyroid malignancy."

Larnygoscope

PET and Genetic Risk of Alzheimer's

Reiman et al. from the Banner Good Samaritan Medical Center (Phoenix, AZ) reported in the June 7 *Proceedings of the National Academies of Sciences* (USA) (2005;102: 8299–8302) on correlations between PET measurements of regional hypometabolism and apolipoprotein E (APOE) epsilon 4 genotype in assessing early Alzheimer's disease (AD). In a previous study in the same journal (2001;98:3334–3339), the authors had described declining brain activity in cognitively normal late middle-aged APOE epsilon 4 carriers, who were found to have abnormally low cerebral metabolic rates for glucose (CMRgl) in the same brain regions (precuneus and posterior cingulate, parietotemporal, and frontal cortices) as patients with probable AD. The current study included 160 cognitively normal individuals aged 47 to 68 years (36 epsilon 4 homozygotes, 46 heterozygotes, and 78 noncarriers) who were assessed with PET. The authors found that the epsilon 4 gene dose (the number of epsilon 4 alleles in the individual's genotype) was inversely correlated with lower CMRgl in each of the AD-associated brain regions. They concluded that these data "raise the possibility of using PET as a quantitative presymptomatic endophenotype to help evaluate the individual and aggregate effects of putative genetic and nongenetic modifiers of AD risk."

Proceedings of the National Academies of Sciences (USA)

PET and CCD in Stroke

In an article e-published ahead of print on June 1 in the *Journal of Cerebral Blood Flow and Metabolism*, Sobesky et al. from the University of Cologne (Germany) reported on the use of PET to study acute crossed cerebellar diaschisis (CCD) and its serial changes after reperfusion in patients who have experienced strokes. The study included 19 patients who received intravenous thrombolysis less than 3 hours after diagnosis of acute stroke. Each underwent ^{15}O-water PET imaging to assess CCD and supratentorial hypoperfusion volume before thrombolysis, at 3 and 24 hours after, and at 14 days. Infarct volume on day 14 and National Institutes of Health Stroke Scale scores at 3 months were recorded. The resulting data indicated that hypoperfusion was correlated to outcome values only at the early stage after stroke. CCD, however, was correlated to outcome values at all assessment time points. The authors concluded that these data suggest that CCD occurs as early as 3 hours after stroke and might be reversible, acute CCD is closely related to the volume of supratentorial hypoperfusion only at early stages but at later stages is strongly associated with outcomes measures, and that PET assessment of CCD adds valuable information to the interpretation of supratentorial reperfusion patterns.

Journal of Cerebral Blood Flow and Metabolism

PET in Panic Disorder

Sakai et al. from the University of Tokyo (Japan) reported in the June 21 issue of *Neuroreport* (2005;16:927–931) on a multinational and multiinstitutional study to assess cerebral glucose metabolism in patients with panic disorder using positron ^{18}F-FDG PET with voxel-based analysis. The study involved PET imaging of 12 nonmedicated patients with panic disorder (who did not experience episodes of panic during acquisition) and 22 healthy individuals. Images of patients with panic disorder (all of whom showed high anxiety before scanning) revealed significantly higher levels of glucose uptake in the bilateral amygdala, hippocampus, thalamus, midbrain, caudal pons, medulla, and cerebellum than did those in the healthy individuals. The authors concluded that these data provided "functional neuro-

imaging support in human patients for the neuroanatomical hypothesis of panic disorder focusing on the amygdala-based fear network."

Neuroreport

PET and Adenomas of the Colon

In an article published in the June 1 issue of the *Journal of Clinical Oncology* (2005;23:3713–3717), van Kouwen et al. from the Radboud University Medical Centre (Nijmegen, The Netherlands) reported on a study designed to determine the utility of ^{18}F-FDG PET in detecting colon adenomas. The study included 100 consecutive patients in whom colon adenomas were suspected on the basis of results from conventional contrast imaging (n = 47) or sigmoidoscopy (n = 53). All patients underwent PET imaging, with positive results defined as focal large bowel tracer accumulation. Colonoscopy was performed after imaging, and histopathologic results from removed adenomas were recorded. Colonoscopy confirmed the presence of adenomas in 68 patients, in 35 of whom PET had identified tracer accumulation at the site of the adenoma. PET sensitivity increased with adenoma size (21% for adenomas 1–5 mm; 47% for those 6–10 mm; and 72% for those larger than 11 mm). PET sensitivity increased with the grade of dysplasia identified at histopathology (33% for low grade; 76% for high grade; and 89% for carcinomas). The overall specificity was 84%. The authors concluded that ^{18}F-FDG PET "detects colonic adenomas and the diagnostic test characteristics improve with size and grade of dysplasia of the adenoma."

Journal of Clinical Oncology

SPECT and Depression After MI

In an article e-published ahead of print in the June 17 issue of *Psychiatry Research*, Schins et al. from the University Hospital Masstricht (The Netherlands) reported on a study using SPECT to assess the pathophysiologic bases of clinical depression in patients after myocardial infarction (MI). They focused on the role of serotonin (5-HT), using SPECT with a ^{123}I-labeled 5-HT(2A) receptor antagonist to study 5-HT(2A) receptor binding. The study included 9 depressed post-MI patients, 10 nondepressed post-MI patients, and 10 healthy control individuals, and results were analyzed using statistical parametric mapping. Depressed post-MI patients showed increased 5-HT(2A) receptor binding compared with nondepressed post-MI patients, and all MI patients showed decreased 5-HT(2A) receptor binding compared with controls. The authors concluded that these data suggest a specific and quantifiable link between seratonin receptor binding and post-MI depression, which in turn suggests avenues of treatment for this frequently noted complication in recovery from cardiac events.

Psychiatry Research

(Continued from page 45N)

- *Develop a standards-setting process for the measurement, analysis, and reporting of biomarker data in association with clinical trials to enhance data comparisons, reduce duplication, and facilitate data submission for regulatory approval.*
- *Investigate integration of phase II trials into the overall prioritization process to further coordinate the national clinical trials system.*

Standardization Initiatives

- *Create, in partnership with the extramural cancer research community, a national cancer clinical trials information technology infrastructure fully interoperable with NCI's cancer Bioinformatics Grid to improve cost effectiveness and comparability of results across trials and sites.*
- *In consultation with industry and FDA, develop standard case report forms incorporating common data elements to improve information sharing among cancer researchers and to optimize data requirements.*
- *Build a credentialing system for investigators and sites recognized by NCI and industry to allow faster trial initiation and keep the investigative community abreast of legal, safety, and regulatory changes.*
- Develop commonly accepted clauses for clinical trial contracts with industry to reduce the lead-time needed to open trials.

Operational Efficiency Initiatives

- *Restructure the phase III funding model to promote rapid patient accrual rates and cost effectiveness.*
- *Reduce institutional barriers to timely trial initiation.*
- Increase patient and public awareness and understanding of clinical trials.
- Increase minority patient access to clinical trials to improve the participation of underserved and underrepresented populations.
- Promote adoption of the NCI Central Institutional Review Board facilitated review process to reduce the time and resources needed to open trials at individual sites.

Enterprise-Wide Initiatives

- *Create a Clinical Trials Oversight Subcommittee of the NCAB to advise the NCI director on conduct of clinical trials across the institute.*
- *Develop a coordinated NCI organizational structure to manage the entire clinical trials enterprise supported by the institute.*

More information about the CTWG can be found at http://integratedtrials.nci.nih.gov. The full report can be found at http://integratedtrials.nci.nih.gov/ict/CTWG_report_June2005.pdf.

National Institutes of Health