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 AND PRACTICE —

Rise in Medical Radiation Exposure Documented

Mettler, from the New Mexico Veterans Affairs Health Care System (Albuquerque), and colleagues from the National Council on Radiation Protection and Measurements (NCRP) Scientific Committee 6-2 medical subgroup reported in the November issue of *Health Physics* (2008;95:501–507) on a wide-ranging survey of radiation exposure in the United States in 2006. The last major reports on this topic, issued by the NCRP in 1987 and 1989, were based on data gathered in 1982 or earlier. The current survey was designed to evaluate the average annual effective dose to members of the U.S. public from medical sources, radon, cosmic and terrestrial radiation, consumer products, and miscellaneous sources. The 6-2 subgroup concentrated its efforts and report summary on medical sources. In 1982, the per capita dose was estimated to be 0.54 mSv and the collective dose to be 124,000 person-Sv. For 2006, the preliminary survey results by the NCRP indicated a per capita dose from medical exposure (not including dental or radiotherapy exposure) at 3.0 mSv and a collective dose at 900,000 person-Sv per year, representing increases of almost 600% and 700%, respectively. CT and nuclear medicine imaging accounted for the largest percentages of these increases. More than 62 million CT procedures performed in the United States in 2006 accounted for 15% of the total number of procedures (excluding dental) and more than half of the collective dose. Nuclear medicine accounted for ~4% of all procedures but 26% of the total collective dose. NCRP charts accompanying the preliminary report indicate that in 1982, nuclear medicine and diagnostic radiology accounted for 15% of total annual radiation exposure to the U.S. population. In 2006, radiography (including fluoroscopy), nuclear medicine, interventional imaging techniques, and CT accounted for 47% of total annual radiation exposure. Additional results from the study are available as a PowerPoint presentation given by NCRP director David Schauer, ScD, on June 6 at the International Society of Radiology in Marrakesh (Morocco) at www.ncrponline.org/PDFs/ICR_2008_DAS.pdf.

National Council on Radiation Protection and Measurements

NOPR Findings on PET During Cancer Treatment

Hillner, from the Virginia Commonwealth University (Richmond, VA), and members of the National Oncologic PET Registry (NOPR) study group reported on November 17 ahead of print in *Cancer* on new data from the NOPR study on the effect of PET on expected management during cancer treatment. NOPR was launched in May 2006 in response to the Centers for Medicare & Medicaid Services' (CMS) "Coverage with Evidence" policy to collect data through a clinical registry to inform ^{18}F-FDG PET coverage determination decisions for currently noncovered cancer indications. As part of its mission, NOPR collected questionnaire data on intended patient management before and after PET in 8,240 patients who underwent 10,497 treatment-monitoring PET scans at 946 centers. The purposes of these studies were to monitor chemotherapy (82%), radiation therapy (6%), or combined-modality treatment (12%). The results indicated that without available PET imaging, these patients would have been assigned to other imaging (53%), ongoing treatment (41%), or biopsy or watching (6%). With the addition of PET, 26%–28% of scans led to a change (switch) in therapies and 16%−19% of scans led to adjustment of therapy dose or length of therapy. Changes in management were more frequent when the referring physician found the post-PET prognosis to be worse than the non-PET prognosis, rather than improved or unchanged. In a striking finding, physicians reported that PET enabled 91% of their patients to avoid some percentage of future tests.

These results in *Cancer* follow several articles on NOPR findings that have brought worldwide attention to the registry's efforts. On November 10, Hillner's group reported online ahead of print in *The Journal of Nuclear Medicine* on NOPR results indicating that information provided by PET affects patient management regardless of cancer type or indication for scanning. Earlier in 2008, the study authors reported in the *Journal of Clinical Oncology* on aggregate NOPR data after 1 y of operation that showed that clinicians changed intended management of more than 1

in 3 cancer patients on the basis of PET findings.

Cancer

PET and Serotonin in Violent Individuals

In the November issue of the *Journal of Psychiatry and Neuroscience* (2008;33:499–508), Meyer et al. from the University of Toronto (Canada) reported on the use of ^{18}F-setoperone PET to investigate prefrontal cortex serotonin 2A ($5HT_{2A}$) binding potential, an index of $5HT_{2A}$ density, in a group of individuals with histories of ongoing violent and aggressive behaviors. The study included 16 participants with such behaviors who were not on medication and 16 healthy control individuals. All participants underwent ^{18}F-setoperone PET imaging to measure $5HT_{2A}$ binding potential in the dorsolateral prefrontal cortex (primarily Brodmann area 9). Significant differences in binding potential were seen in the study and control groups. Results indicated that prefrontal cortex $5HT_{2A}$ binding potential was significantly lower in participants with more severe impulsivity and aggression than in those with milder aggression or in controls. The authors concluded that lower prefrontal $5HT_{2A}$ binding potential is related to violent aggression, adding that lower $5HT_{2A}$ binding potential "occurs at a younger age, when violent behavior is more frequent, and is more prominent when impulsivity and aggression are more severe."

Journal of Psychiatry and Neuroscience

PET Images Multidrug Resistance–Associated Protein 1

Okamura et al. from the National Institute of Radiological Sciences (Chiba, Japan) reported on November 5 ahead of print in the *Journal of Cerebral Blood Flow and Metabolism* on a small animal PET technique for noninvasive, quantitative assessment of the function of multidrug resistance–associated protein 1 (MRP1) in the living brain. A 6-bromo-7-^{11}C-methylpurine probe was designed to enter the brain after intravenous administration and efficiently convert to its glutathione conjugate (MRP1 substrate). Brain time–activity curves derived from PET imaging with this tracer estimated the efflux rate of the substrate at 1.4 h. Along with the finding that use of mice with the MRP1 knockout gene resulted in a 90% reduction of the efflux rate compared with rates in wild-type mice, this approach appears to overcome previous limitations for studying MRP1 brain-to-blood efflux. The authors concluded that "our method allows noninvasive and quantitative assessment for MRP1 function in the living brain."

Journal of Cerebral Blood Flow and Metabolism

Imaging Choices in MTC

On November 12, ahead of print in *Endocrine-Related Cancer*, Faggiano et al. from the Federico II University (Naples, Italy) reported on a study investigating whether clinico-biologic profiles can suggest optimal imaging techniques for postoperative identification of persistent or relapsing medullary thyroid carcinoma (MTC). The study included 35 patients with MTC who had detectable and progressively increasing postoperative serum concentrations of calcitonin. Patients underwent ^{18}F-FDG PET, somatostatin receptor scintigraphy (SRS), and ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, and imaging results were compared with calcitonin and carcinoembryonic antigen serum concentrations, Ki-67 scores, and results of conventional imaging techniques. The research showed that positive PET findings were significantly associated with calcitonin serum concentrations >400 pg/mL and Ki-67 scores >2.0%. Positive SRS findings were associated with calcitonin serum concentrations >800 pg/mL and correlated significantly with tumor appearance on conventional imaging. PET findings were positive in 9 patients whose conventional imaging results were negative. ^{131}I-MIBG scintigraphy was not correlated with clinico-biologic profiles. The authors concluded that secretive and proliferative tumor profiles may guide the choice of most useful imaging technique in follow-up of patients with MTC and that a Ki-67 score >2.0% suggests the need for PET in addition to conventional imaging.

Endocrine-Related Cancer

PET in Early Pancreatic Carcinoma

Seo et al. from Kyoto University (Japan) reported in the November–December issue of the *Journal of Hepatobiliary and Pancreatic Surgery* (2008;15:634–639) on a study investigating the potential contributions of ^{18}F-FDG PET in early pancreatic cancer. The study included 56 patients with early pancreatic cancer who underwent PET imaging and curative surgery. Standardized uptake values (SUVs) were compared with clinicopathologic results. Tumors ranged from 0.8 to 6.5 cm in diameter. When the SUV cutoff value was set at 2.5, 51 of the 56 patients (91%) had positive PET imaging studies. SUVs were not correlated with tumor differentiation, primary/nonprimary status, or maximum tumor diameter. SUVs in 5 tumors were below the cutoff value, and each of these tumors had intermediate or scirrhous stroma rather than medullary stroma. The authors concluded that these results suggest that ^{18}F-FDG PET is "useful for the detection of small early pancreatic cancers."

Journal of Hepatobiliary and Pancreatic Surgery

Adrenal Scintigraphy in Incidentaloma Follow-Up

Fagour et al. from University Hospital of Bordeaux (Pessac, France) reported on October 3 ahead of print in the *European Journal of Endocrinology* on a study assessing the utility of ^{131}I-6-β-iodomethylnorcholesterol scintigraphy in predicting the occur-

rence of progression in incidentally discovered benign adrenal cortical adenomas. The multicenter study included 51 patients with unilateral adrenal cortical adenomas and normal 24-h urinary free cortisol. All patients underwent scintigraphy and were followed for 4.3 ± 1.6 y. At baseline assessment, biochemically defined subclinical Cushing's syndrome (SCS) was found in 47% of patients, and unilateral uptake was significantly associated with SCS. Over the course of the follow-up period, hormone assessments remained unchanged in 53% of patients, 29% displayed intermittent SCS, and 18% showed definitive hormonal progression of SCS but without overt biochemical hypercortisolism. Unilateral uptake was associated with persistence of SCS and hormonal progression. Tumor size increased in 10% of patients and was not associated with any scintigraphic pattern. The authors concluded that evolution of SCS toward overt biochemical Cushing's syndrome in patients with adrenal cortical adenomas is rare during a 4-y follow-up and that unilateral uptake on scintigraphy is "predictive for the occurrence of SCS, its persistence, and progression within the spectrum of SCS." They added that additional studies will be necessary to determine the effects of management decisions based on this scintigraphic approach on clinical outcomes.

European Journal of Endocrinology

Preoperative Plus Postoperative Imatinib in GIST

On October 25, McAuliffe et al. from the University of Texas–Houston reported ahead of print in the *Annals of Surgical Oncology* on a randomized phase II study to assess the safety and efficacy of postoperative imatinib mesylate (imatinib) for the treatment of gastrointestinal stromal tumor (GISTs). The study included 19 patients undergoing surgical resection for GIST. Patients were assigned to groups receiving 3, 5, or 7 d of preoperative imatinib, and all patients received postoperative imatinib for 2 y. All patients underwent serial ^{18}F-FDG PET, dynamic CT, and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay, and disease-free survival was noted. Imatinib was not associated with adverse events at surgery or immediately thereafter when results were compared with those from similar patients who underwent resection for GIST without imatinib. PET and CT imaging indicated that ~70% of patients responded to preoperative imatinib. Preoperative administration also resulted in an average 12% increase in tumor cell apoptosis, which correlated with the duration of preoperative imatinib. For patients treated with both pre- and postoperative imatinib, median disease-free survival was 46 mo. Tumor size was found to be a significant predictor of recurrence. The authors concluded that "imatinib appears to be safe and may be considered for patients undergoing surgical resection of their GIST." They added that imaging may play a special role in determining appropriate follow-up treatments, because radiographic responses and tumor cell apoptosis occur within the first week of imatinib therapy.

Annals of Surgical Oncology

THERAPY

Chemo Plus RIT in Follicular Lymphoma

Jacobs et al. from the University of Pittsburgh Medical Center Cancer Centers (PA) reported in the November 1 issue of *Clinical Cancer Research* (2008;14:7088–7094) on a study designed to determine the complete response rate in patients with previously untreated follicular lymphoma to short-course chemoimmunotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R) followed by ^{90}Y-ibritumomab tiuxetan radioimmunotherapy (RIT) with extended rituximab as a first-line treatment. The study included 60 patients with stages II–IV symptomatic or bulky follicular lymphoma who received CHOP-R for 3 treatment cycles before RIT followed by 4 additional weekly treatments with rituximab. All patients underwent serial PET and CT imaging to assess effectiveness during an average follow-up of 19.7 mo. Fifty-five patients completed all protocol therapies. The PET- and CT-determined complete response rates after CHOP-R were 40% and 46%, respectively. With the addition of RIT, the complete response rates improved on PET and CT assessment to 82% and 89%, respectively. Ten patients later progressed, including 8 who were assessed as having complete responses. Seven of 18 patients who were PET positive after chemotherapy progressed, compared with only 3 of 37 patients in whom PET findings were negative. The authors concluded that these results suggest that short-course chemoimmunotherapy, consolidation RIT, and extended rituximab constitute a promising approach in patients with previously untreated, symptomatic, or bulky follicular lymphoma. They added that "failure to achieve an early PET complete response after CHOP-R indicated high risk of relapse."

Clinical Cancer Research

Integrin $\alpha_v\beta_3$ RIT in Glioblastoma Multiforme

Veeravagu et al. from Stanford University School of Medicine (CA) and Peking University (Beijing, China) reported in the November 15 issue of *Clinical Cancer Research* (2008;14:7330–7339) on a study evaluating both the efficacy of a novel ^{90}Y-abegrin radioimmunotherapy (RIT) agent in mice with xenografted glioblastoma and the ability of PET to monitor the molecular effects of treatment. Integrin $\alpha_v\beta_3$ abegrin is a monoclonal antibody to human integrin $\alpha_v\beta_3$, which is highly expressed on glioblastoma multiforme tumor cells. The researchers determined the maximum tolerated treatment dose, biodistribution, dose

response, and efficacy in the human glioblastoma xenograft mouse model and in a mouse model of a low integrin–expressing cancer. A maximum tolerated dose of 200 μCi was found to have good hepatic clearance and cause no organ toxicity. Glioblastoma mice showed partial regression of tumor volume, whereas other groups did not. ^{18}F-FDG PET showed reduced cell proliferation and metabolic activity in these tumors, and ^{18}F-FLT PET indicated decreased DNA synthesis. In these same animals, Ki-67 analysis showed reduced proliferative index, and additional analysis showed increased DNA fragmentation, apoptosis, vascular fragmentation, and dysmorphic vessel structure. The authors concluded that RIT with ^{90}Y-abegrin "may prove promising in the treatment of highly vascular, invasive, and heterogeneous malignant brain tumors."

Clinical Cancer Research

MOLECULAR IMAGING

Thyroid Imaging Targeting Galectin-3

Bartolazzi et al. from the Karolinska Hospital (Stockholm, Sweden) reported online on November 20 in *PLoS ONE* on a small animal study using ^{99m}Tc-labeled galectin-3–based thyroid immunoscintigraphy to provide discriminatory in vivo imaging of thyroid cancer. Discrimination between benign and malignant thyroid nodules is difficult with conventional thyroid scintigraphy. Only cancer cells express the antiapoptotic molecule galectin-3, making it a suitable target to explore the possibility for more accurate preoperative assessment of patients with thyroid nodules. The study included 38 mice with human galectin-3–positive thyroid cancer xenografts and galectin-3 knockout tumors. Over several experiments, the mice were injected with a ^{99m}Tc-labeled monoclonal antibody to galectin-3. Mice were imaged with a position-sensitive high-resolution mini gamma camera at 1, 3, 6, 9, and 24 h after injection. Optimal visualization of thyroid cancer xenografts was obtained between 6 and 9 h after injection, and no galectin-3–negative tumors were visible. The authors concluded that these results suggest "the possibility to distinguish preoperatively benign from malignant thyroid nodules by using a specific galectin-3 radio-immunotargeting." In addition to enhancing selection of appropriate patients for surgery, they discussed the possibility of applying this technique in the treatment and imaging of other galectin-3–expressing tumors.

PLoS ONE

Novel Detection of Airway Inflammation

Cortez-Retamozo et al. from the Massachusetts General Hospital and Harvard Medical School (Boston, MA) reported on November 6 ahead of print in the *Journal of Clinical Investigation* on the use of an injectable matrix metalloproteinase–targeted optical sensor for real-time assessment of inflammation and treatment response in a mouse model of allergic airway inflammation. The optical sensor targeted and quantified eosinophil activity in the lungs of mice with experimental allergic airway inflammation. Several imaging techniques were used to visualize eosinophil responses. Near-infrared fluorescence fiberoptic bronchoscopy yielded images at single-cell resolution in conducting airways. Intravital microscopy was used in lung parenchyma, and fluorescence-mediated molecular tomography was used for whole-body imaging. As evidence of the utility of this approach, the authors confirmed the immunosuppressive effects of the glucocorticoid drug dexamethasone in this mouse model and identified a viridin-derived prodrug that inhibited the accumulation and enzyme activity of eosinophils in the lungs. They concluded that this combination of "sensitive enzyme-targeted sensors with noninvasive molecular imaging approaches permitted evaluation of airway inflammation severity" and was successful as a model that could be used for rapid screening of new drug effects.

Journal of Clinical Investigation

Targeted Gold Nanoparticles for Molecular CT

Popovtzer and colleagues from the University of Michigan (Ann Arbor) reported on November 5 ahead of print in *Nano Letters* on a targeted molecular imaging platform based on gold nanoprobes that enables cancer detection at the cellular and molecular levels with standard clinical CT. The nanoprobes were described as selectively and sensitively targeting tumor-elective antigens while inducing distinct contrast in CT imaging. The authors offered an in vitro proof-of-principle demonstration in head and neck cancer, with results indicating that the attenuation coefficient for the molecularly targeted cells was >5 times higher than for untargeted cancer cells or normal cells. They concluded that this novel imaging tool could "lead to significant improvements in cancer therapy due to earlier detection, accurate staging, and micro-tumor identification."

Nano Letters

Magnetic Nanocarriers Target Pancreatic Islets

Medarova et al. from the Massachusetts General Hospital and Harvard Medical School (Charlestown, MA) reported in the November 15 issue of *Transplantation* (2008;86:1170–1177) on a novel technology centered on multifunctional magnetic nanocarriers that deliver small interfering RNA (siRNA) molecules to intact pancreatic islets and at the same time facilitate monitoring with MR and optical imaging. The technique is part of a larger strategy aimed at modifying the genetic profile of the beta cell as a means for managing metabolic dysregulation and thereby providing curative approaches to diabetes. Magnetic nanoparticles carrying siRNA designed to target a model gene for

enhanced green fluorescent protein were efficiently taken up by murine pancreatic islets and were easily visualized with MR and near-infrared fluorescence optical imaging. The result was the suppression of the target gene. The authors concluded that these results "illustrate the value of our approach in overcoming the challenges associated with genetic modification of intact pancreatic islets in a clinically acceptable manner," with the additional advantage of the combined capability of the nanoparticles to precisely deliver siRNA and to magnetically label pancreatic islets.

Transplantation

Tracking Inflammatory Response in Stroke

On November 14, Breckwoldt et al. from the Harvard Medical School (Charlestown, MA) reported ahead of print in the *Proceedings of the National Academy of Sciences of the United States of America* on a functional, enzyme-activatable MR imaging agent designed to accurately track the oxidative activity of myeloperoxidase, a key inflammatory enzyme secreted by activated neutrophils and macrophages/microglia, in stroke in living animals. Using their novel technique, the researchers found myeloperoxidase to be widely distributed in ischemic tissues, positively correlated with infarct size, and detectable as late as 3 wk after stroke. Peak levels of myeloperoxidase were detected at 3 d after ischemia. The technique tracked myeloperoxidase activity and confirmed inflammation on the molecular level in vivo, information that the authors noted "was previously only possible to obtain on ex vivo brain sections and impossible to assess in living human patients." They added that these findings could allow "efficient and noninvasive serial screening of therapies targeting inflammation and the use of myeloperoxidase imaging as an imaging biomarker to risk-stratify patients."

Proceedings of the National Academy of Sciences of the United States of America

Advances in ^{19}F MR Molecular Imaging

The stable isotope ^{19}F, which has been used in a variety of MR investigations for more than 2 decades, remains the focus of considerable research that increasingly looks at molecular-level results in diagnosis and therapy. In the November issue of *Magnetic Resonance in Medicine* (2008;60:1066–1072), Neubauer et al. from Washington University (St. Louis, MO) reported on a new strategy for MR imaging using gadolinium-modulated ^{19}F signals from perfluorcarbon nanoparticles. Gadolinium was directly incorporated as a relaxation agent into the lipid monolayer surrounding the perfluorocarbon in the 200-nm nanoparticles. The result was marked enhancement of the ^{19}F signal, a 4-fold increase in the magnetic relaxation rate of the ^{19}F nuclei at 1.5 T, and a 125% increase in signal. The relaxation effect could also be quantitatively modulated to tailor particle properties by varying the surface concentration of gadolinium. The authors concluded that this strategy "dramatically improves the sensitivity and range of ^{19}F MR imaging/MR spectroscopy and forms the basis for designing contrast agents capable of sensing their surface chemistry."

In an article in the December 7 issue of *Physics in Medicine and Biology* (2008;53:6979–6989), Porcari et al. from the University of Rome "Sapienza" (Italy) reported on a new approach using ^{19}F MR and MR spectroscopy to optimize boron neutron capture therapy (BNCT) in the treatment of malignant brain gliomas. In BNCT, boronated phenylalanine is infused into the patient and subsequently exposed to neutron irradiation, releasing short-range α radiation and "recoil" lithium in tumor cells, resulting in highly localized radiation-induced apoptosis. By labeling the boronophenylalanine with ^{19}F, the authors selectively mapped in vivo spatial distribution and pharmacokinetics using MR and MR spectroscopy in a rat glioma model. Maximum uptake occurred at 2.5 h after infusion into the animals. This approach could be useful in estimating optimal timing for neutron irradiation in BNCT and in providing a method for performing pharmacokinetic studies of other BNCT carriers.

Magnetic Resonance in Medicine
Physics in Medicine and Biology

(Continued from page 18N)

2008. Proposed changes to the radiopharmaceutical payment methodology cannot be implemented until January 1, 2010.

The 2009 MPFS final rule also implements requirements mandated by the 2008 MIPPA legislation. This bill replaces the anticipated 15.1% payment cut with an overall 1.1% increase to physician payments. Most important, this final rule does not change the radiopharmaceutical payment methodology in the physician office or Independent Diagnostic Testing Facility (IDTF) for 2009. Drugs, contrast agents, and biologicals also will continue to be paid at 106% of the average sales price (ASP+6).

In keeping with the requirements of the Deficit Reduction Act, this final rule continues to cap payment rates for imaging services under the physician fee schedule at the amount paid for the same services when performed in hospital outpatient departments. Twenty nuclear medicine codes are affected by this policy in 2009.

In addition to payment rate setting, the 2009 MPFS final rule implements a few quality-related initiatives. First, CMS did not finalize the proposal to require that physicians who furnish diagnostic testing services meet the quality and performance standards required for IDTFs. CMS will revisit this proposal at a later time, if necessary. Second, CMS finalized 153 measures for 2009 reporting. Included in these measures is 1 nuclear medicine bone scan imaging measure. The rule can be reviewed at the SNM Coding Corner Web site (www.snm.org/codingcorner).

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