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

^{99m}Tc-DMSA Scintigraphy in Pediatric UTI

Two articles e-published in October ahead of print focused on the consequences of pediatric urinary tract infections (UTIs) and efforts to assess risk factors for recurrence and complications. Both used ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy in exploring the characteristics of UTI in infants and children. Kotoula et al. from the Democritus University of Thrace School of Medicine (Alexandroupolis, Greece) reported on October 3 in *International Urology and Nephrology* on a study designed to establish the most reliable markers for identifying renal parenchymal involvement in UTIs in a group of 57 children (ages, 2–108 mo) admitted for a first episode of UTI. Among the markers evaluated were clinical features, admission leukocyte count, erythrocyte sedimentation rate, C-reactive protein, and serum procalcitonin. Results were compared with the presence (27 children) or absence (30 children) of renal parenchymal involvement as determined by ^{99m}Tc-DMSA imaging. The authors found that serum procalcitonin had the best performance as an early predictive marker of renal parenchymal involvement, with sensitivity, specificity, and positive and negative predictive values of 89%, 97%, 96%, and 91%, respectively.

Shim et al. from the Ewha Womans University School of Medicine (Seoul, Korea) reported online on October 2 in *Pediatric Nephrology* on a study assessing risk factors for recurrent UTIs and subsequent renal scarring in infants with normal urinary systems. The study included 190 infants diagnosed with a first UTI. Along with UTI recurrence and other clinical features, the researchers gathered data on sex, age, phimosis, vaginal reflux, and acute pyelonephritis as assessed by ^{99m}Tc-DMSA scintigraphy. The recurrence rate within 1 y was 21.1%, with a significantly higher rate among children <6 mo old (25.8%) than among those older (7.7%). In an incidental finding, the authors noted that recurrent UTI was seen in 34.0% of male infants with persistent nonretractile prepuces, a percentage significantly higher than the 17.6% recurrence rate in other male infants. The authors concluded that for infants with normal urinary tract systems, the most significant factors for recurrence of a first UTI were age <6 m and the presence of a nonretractile prepuce and/or acute pyelonephritis in males. They suggested that "nonretractile prepuces should be adequately treated to become retractile in young male infants with acute pyelonephritis."

International Urology and Nephrology
Pediatric Nephrology

Recurrence Patterns in PET-Staged Colorectal Metastases

Finkelstein et al. from Washington University in St. Louis (MO) and the affiliated Barnes-Jewish Hospital reported in the September issue of the *Journal of Hepato-Biliary-Pancreatic Surgery* (2008;15:483–487) on additional data stemming from a previously reported study showing excellent 5-y survival rates in patients staged with ^{18}F-FDG PET before liver resection for metastatic colorectal cancer (*Ann Surg.* 2004;240:438–447). The current study focused on site- and time-specific patterns of recurrence in these patients and compared the results with control data derived from a literature search of all published case series of conventionally staged patients. The study included 100 patients who underwent ^{18}F-FDG PET before hepatic resection for colorectal cancer metastases. Of these, 48 patients had no evidence of recurrence, 30 had recurrence within 1 y of resection, and 22 had recurrence after 1 y. Of those who had recurrence within 1 y, 70% experienced intrahepatic recurrence, whereas 86% of patients with recurrence >1 y after resection had extrahepatic recurrence, a pattern that was not to be found in reports of conventionally staged patients. The authors posited 2 potentially converging factors to explain the difference in pattern results in PET and conventional staging: (1) that ^{18}F-FDG PET more effectively detects extrahepatic disease than conventional staging; and (2) that liver resection may contribute to a growth spurt in hepatic metastases.

Journal of Hepato-Biliary-Pancreatic Surgery

Prestransplant PET in Aggressive B-Cell NHL

In an article e-published on October 2 ahead of print in *Cancer*, Derenzini et al. from the University of Bologna (Italy) reported on a study designed to identify the main determinants of prognosis in patients with aggressive B-cell non-Hodgkin's lymphoma (NHL) who undergo autologous stem cell transplantation. Among the factors considered were pretransplantation ^{18}F-FDG PET, secondary age-adjusted International

Prognostic Index score, histology, and previous response to first-line chemotherapy. The study included 75 patients with diffuse, large B-cell lymphoma or grade 3 follicular lymphoma who were treated with second-line chemotherapy followed by autologous stem cell transplantation (in only 72 patients). All patients underwent PET imaging after 1–3 courses of chemotherapy and before stem cell transplantation. Subsequent analyses determined that pretransplantation PET was the only significant independent prognostic factor for progression-free survival and overall survival.

Cancer

^{11}C-Methionine PET in Liver Transplantation

Otsuki et al. from the National Chiba-East Hospital (Japan) reported in the October issue of *Transplantation Proceedings* (2008;40:2562–2564) on the utility of ^{11}C-methionine PET for the evaluation of segmental pancreatic function before and after distal pancreatectomy in patients with pancreatic disease and in living donors for pancreas transplantation. In each individual, tracer uptake by the pancreatic head was expressed as a standardized uptake value (SUV), with comparisons between pre- and postsurgical SUVs. Before distal pancreatectomy, the SUVs of the pancreatic head in patients and donors were 15.3 ± 6.0 and 16.1 ± 1.0, respectively. These respective SUVs were 18.2 ± 2.4 and 14.7 ± 1.4 after surgery. Although no significant differences were noted after surgery in either group, the SUVs of the residual pancreatic head were elevated in 80% of patients and 50% of donors. The authors concluded that these data suggest that "the function of the pancreatic head may be maintained or improved after distal pancreatectomy" and that ^{11}C-methionine PET may become "a potent modality to evaluate segmental pancreatic function for a safe living donor operation."

Transplantation Proceedings

PET in NHL Bone Marrow Involvement

In the October issue of the *American Journal of Clinical Oncology* (2008;31:409–412), Muslimani et al. from the Cleveland Clinic at Fairview Hospital (OH) reported on the use of ^{18}F-FDG PET to accurately assess the presence of bone marrow involvement in non-Hodgkin's lymphoma (NHL). The study included 97 patients with histologically proven NHL. Each patient underwent ^{18}F-FDG PET imaging for initial staging, as well as unilateral posterior iliac crest bone marrow biopsy. The authors found an overall sensitivity and specificity for ^{18}F-FDG PET of 79% and 91%, respectively, in detecting bone marrow involvement, regardless of the type of NHL (indolent or aggressive/highly aggressive). They concluded that ^{18}F-FDG PET shows potential for the routine detection of bone marrow involvement in NHL. They noted that image-guided repeat bone marrow biopsy should be considered in patients with negative initial iliac crest bone marrow biopsy and whose PET scans show bone marrow involvement in a different site.

American Journal of Clinical Oncology

PET in Oral Cavity Squamous Cell Carcinoma

Liao et al. from Chang Gung Memorial Hospital and Chang Gung University (Taoyuan, Taiwan) reported on October 2 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics* on the capabilities of primary tumor standardized uptake values (SUVs) obtained on preoperative ^{18}F-FDG PET imaging to predict outcomes in patients with oral cavity squamous cell carcinoma and pathologically positive lymph nodes. The study included 109 such patients who underwent ^{18}F-FDG PET imaging within 2 wk before surgery and neck dissection, with 24-mo follow-up or death within that period as endpoints (26-mo median follow-up for all patients; 39 mo for surviving patients). An SUV_{max} of 19.3 and tumor depth $\geq$12 mm provided the greatest prognostic information for the 5-y local control rate. The authors found that the 8 patients with both an $SUV_{max} \geq 19.3$ and tumor depth $\geq$12 mm had significantly poorer 5-y local control, disease-free, disease-specific, and overall survival rates than other patient groups. They concluded that the combination of primary tumor SUV_{max} and pathologic tumor depth was able to identify "a subgroup of oral cavity squamous cell carcinoma patients at greatest risk of poor local control and death."

International Journal of Radiation Oncology, Biology, Physics

PET and Laparoscopy in Recurrent Ovarian Cancer

In an article published in the October 1 issue of *Oncology* (2008;75:152–158), Fagotti et al. from the Catholic University of the Sacred Heart (Rome, Italy) reported on a study investigating the roles of ^{18}F-FDG PET/CT and laparoscopy in optimal diagnostic and staging strategies for recurrent ovarian cancer. The study included 70 patients with recurrent ovarian cancer who underwent both PET/CT and laparoscopy. Negative and positive predictive values, specificity, sensitivity, and accuracy rates with each technique were compared, as were the numbers of nodules accurately identified. The negative and positive predictive values, specificity, sensitivity, and accuracy of PET/CT were 83.3%, 76.9%, 55.6%, 93.0%, and 78.6%, respectively. Corresponding respective values for staging laparoscopy were 88.9%, 64.0%, 80.8%, 95.0%, and 83.1%. Combined, the 2 techniques showed negative and positive predictive values of 88.9% and 78.8%, respectively, and specificity, sensitivity, and accuracy of 59.3%, 95.3%, and 81.4%, respectively. Staging laparoscopy was more capable than PET in identifying involved nodules (50.0% and 40.3%, respectively). The authors concluded that the combination of PET/CT and staging laparoscopy "has a significant effect on the multimodal approach to the population of patients with recurrent ovarian cancer" and that "such techniques should be considered complementary" because of the potential of each in different settings of the disease.

Oncology

Post-RT PET in Head and Neck Cancer

Yao et al. from the University Hospitals Case Medical Center (Cleveland, OH) reported on October 16 in the *International Journal of Radiation Oncology, Biology, Physics* on the accuracy and long-term prognostic abilities of ^{18}F-FDG PET in squamous cell carcinoma of the head and neck after radiation therapy. The study included a retrospective review of the records of 188 patients with head and neck squamous cell carcinoma who had undergone PET imaging within 1 y of intensity-modulated radiation therapy (128 with definitive and 60 with postoperative intensity-modulated therapy). Median follow-up times after radiation therapy and PET imaging were 32.6 and 29.2 mo, respectively. PET findings in the neck were negative in 171 (2 false-negative) and positive in 17 (12 true-positive) patients. Sensitivity, specificity, and positive and negative predictive values in assessment of treatment response in the neck were 86%, 97%, 71%, and 99%, respectively. PET findings in the primary site were negative in 151 patients (2 false-negatives) and positive in 37 patients (12 true-positives). Sensitivity, specificity, and positive and negative predictive values in assessment of treatment response in the primary site were 86%, 86%, 32.4%, and 98.7%, respectively. Patients with positive PET findings after radiation therapy had significantly worse 3-y overall survival and disease-free survival rates. The authors concluded that these results suggest that PET has a high negative predictive value and "can provide guidance for the management of head-and-neck cancer after definitive treatment."

International Journal of Radiation Oncology, Biology, Physics

THERAPY

Derlin-1 Role in Tumor-Targeting Therapy

Ran et al. from the Peking Union Medical College (Beijing, People's Republic of China) reported in the October 15 issue of *Clinical Cancer Research* (2008;14:6538–6545) on a study of the potential role of the channel-like protein derlin-1 in antibody-mediated tumor targeting therapy. The authors first demonstrated the cell surface expression of derlin-1 with immunofluorescent analysis of nonpermeabalized cells and Western blotting of fractional proteins of tumor cells. Immunochemistry confirmed derlin-1 expression in cancerous tissues. After the protein was radiolabeled with ^{125}I, biodistribution analyses and scintigraphy were performed in injected isogenic mice models. Tumor-bearing mice were treated with anti-derlin-1 poly- and monoclonal antibodies. Although robust cytoplasmic and membrane expression of derlin-1 was detected in various types of human cancer tissues, this was not correlated with the clinicopathologic features of pancreatic cancer. Derlin-1–directed antibodies successfully targeted colon tumors and significantly suppressed tumor growth. The authors concluded that these preclinical data showed "that derlin-1 protein is a functional molecular target expressed on the tumor cell surface and is a candidate therapeutic target that may be translated into clinical applications."

Clinical Cancer Research

Enhancing ^{177}Lu-Based RIT in Protate Cancer

In an article e-published on October 21 ahead of print in *Prostate*, Kelly et al. from the Austin Hospital (Heidelberg, Australia) reported on a study exploring the biodistribution and therapeutic efficacy of ^{177}Lu-labeled anti-Lewis Y monoclonal antibody hu3S193 radioimmunotherapy (RIT) in mice bearing prostate cancer xenografts. In addition, potential enhancements provided by the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor AG1478 and by docetaxel chemotherapy were assessed. The cytotoxicity of the radiolabeled agent was assessed using proliferative assays in Lewis-Y positive DU145 prostate cancer cells, and induction of apoptosis was measured by enzyme-linked immunosorbent assay. Results showed that ^{177}Lu-hu3S193 mediated significant induction of cytotoxicity and apoptosis. Both biodistribution and tumor localization of the agent were studied in mice bearing DU145 tumor xenografts, with a dose escalation study used to assess efficacy and maximum tolerated dose. These mouse studies showed specific targeting of DU145 prostate cell xenografts, with maximum tumor uptake of 33.2 $\pm$ 3.9 %ID/g at 120 h after injection. ^{177}Lu-hu3S193 caused specific and dose-dependent inhibition of prostate cancer tumor growth, with a maximum tolerated dose of 350 μCi. When either EGFR inhibitor AG1478 or docetaxel chemotherapy was administered at subtherapeutic doses with RIT, efficacy was significantly improved. The authors concluded that "^{177}Lu-hu3S193 RIT is effective as a single agent in the treatment of Lewis-Y positive prostate cancer models" and that the "enhancement of RIT by AG1478 or docetaxel indicates the promise of combined modality strategies."

Prostate

MOLECULAR IMAGING

Imaging T–B Cell Interactions

Qi et al. from the National Institute of Allergy and Infectious Diseases (Bethesda, MD) reported in the October 9 issue of *Nature* (2008;455:764–769) on a study using 2-photon intravital imaging to explore the mechanisms underlying defects in germinal center formation, a crucial element in the generation of long-term antibody-mediated immunity that involves cooperation between antigen-specific T and B lymphocytes. Molecular imaging indicated that loss-of-function mutations in the signaling lymphocyte activation molecule–associated protein and resulting deficiencies selectively impaired the ability of T cells to stably interact with cognate B cells but not with antigen-presenting dendritic cells. These loss of function mutations are common in human X-linked lymphoproliferative disease and the gene-

targeted mouse model explored in this study, and result in a failure of antigen-specific B cells to receive adequate levels of contact-dependent T-cell help to expand normally. In addition, the lack of stable interactions with B cells renders signaling lymphocyte activation molecule–associated protein T cells unable to be efficiently recruited to and retained in a nascent germinal center as part of the germinal center reaction. The authors concluded that these results "offer an explanation for the germinal center defect due to signaling lymphocyte activation molecule–associated protein deficiency and provide new insights into the bidirectional communication between cognate T and B cells in vivo."

Nature

MR and Integrin-Targeted Nanoparticles in Angiogenesis

Waters et al. from the Washington University School of Medicine (St. Louis, MO) reported on September 25 ahead of print in the *Journal of Cardiovascular Magnetic Resonance* on a study of the specific binding of $\alpha_v\beta_3$ integrin–targeted nanoparticles to neovasculature in a rabbit model of aortic valve disease. The study also focused on the ability of fluorine-labeled MR techniques to detect and quantify neovasculature in excised valve leaflets. The experiment included 16 New Zealand white rabbits that were cholesterol fed for ~6 mo to promote the development of aortic valve thickening, inflammation, and angiogenesis mimicking early human aortic valve disease. Ten animals were treated with $\alpha_v\beta_3$ integrin–targeted perfluorocarbon nanoparticles, and 6 controls were treated with untargeted perfluorocarbon nanoparticles. At 2 h after treatment, the aortic valves were removed from 6 of the integrin-targeted animals and all 6 of the control animals. The valves were imaged with ^{19}F MR spectroscopy. The remaining 3 rabbits treated with $\alpha_v\beta_3$ integrin–targeted nanoparticles underwent ^{19}F MR spectroscopy on a clinical scanner. All results were compared with angiogenesis determined by immunohistochemistry. The researchers found that the valves of animals treated with targeted nanoparticles had 220% more fluorine signal than those of animals treated with untargeted nanoparticles. Nanoparticles were also successfully detected in all samples scanned on the clinical scanner. Immunohistochemistry confirmed the presence of angiogenesis in all sampled valves. The authors concluded that because these integrin-targeted nanoparticles specifically detect early angiogenesis in sclerotic aortic valves of cholesterol-fed rabbits, these techniques "may be useful for assessing atherosclerotic components of preclinical aortic valve disease in patients and could assist in defining efficacy of medical therapies." They added that although questions remain about specifically what to image as meaningful biomarkers of early valve disease, a variety of molecules and cell types are potentially targetable and may prove complementary in elucidating complex pathologies.

Journal of Cardiovascular Magnetic Resonance

IL-18–Binding Protein-Fc Therapy

In an article in the October 1 issue of *Clinical Cancer Research* (2008; 14:6137–6145), Cao et al. from the Stanford University School of Medicine (CA) reported on a study designed to use multimodality molecular imaging to identify cell lines that are most sensitive to standalone interleukin-18–binding protein (IL-18bp)-Fc treatment, to study the pharmacokinetics and tumor targeting efficiency of IL-18bp-Fc, and to assess the efficacy of IL-18bp-Fc in treating experimental breast cancer metastases to the lung. A range of murine cells were assayed to determine that 4T1 cells had the greatest sensitivity to IL-18bp-Fc. 4T1 cells were stably transfected with firefly luciferase and injected into mice to establish an experimental lung metastasis model. Animals underwent ^{64}Cu-DOTA-IL-18bp-Fc PET to assess biodistribution, pharmacokinetics, and tumor targeting efficiency. Animals were divided into 2 groups and administered either intraperitoneal saline or IL-18bp-Fc daily. Animals then underwent bioluminescence imaging, ^{18}F-FDG PET, and CT imaging to assess treatment results. These results were compared with histopathology and other ex vivo studies. The researchers found that PET showed high and specific IL-18bp-Fc accumulation in the luciferase-injected 4T1 lung metastasis tumors and that all 3 imaging modalities indicated that IL-18bp-Fc treatment was effective in inhibiting lung metastasis tumor progression. The authors concluded that IL-18bp-Fc therapy can inhibit experimental breast cancer lung metastasis and that "noninvasive multimodality molecular imaging is a powerful tool for evaluating the tumor targeting efficiency/pharmacokinetics of the drug and effective monitoring of the therapeutic response."

Clinical Cancer Research

Imaging MMPs in Vascular Remodeling

Zhang et al. from the Yale University School of Medicine (New Haven, CT), the VA Connecticut Healthcare System (West Haven), and Lantheus Medical Imaging (North Billerica, MA) reported on October 20 ahead of print in *Circulation* on a study of ^{111}In-labeled molecular imaging of activated matrix metalloproteinases (MMPs) in vascular remodeling. RP782, a novel indium ^{111}In-labeled tracer with specificity for activated MMPs, was used to detect injury-induced vascular remodeling in a mouse model. Carotid wire injury was induced in 1 group of apolipoprotein $E^{-/-}$ mice, with sham surgery performed in controls. Carotid wire injury led to significant hyperplasia and remodeling over the following 4 wk. MMP activity, detected by in situ zymography, increased after injury, reaching a maximum at 3–4 wk. Mice were imaged with RP782 microSPECT and CT angiography at 1, 2, 3, and 4 wk after carotid injury or sham surgery. Focal uptake of RP782 was seen in the injured artery on

microSPECT at 2, 3, and 4 wk. Pretreatment with excess nonlabeled tracer significantly reduced RP782 uptake, indicating uptake specificity. Serial changes in the vessel wall area correlated closely with RP782 uptake. The authors concluded that RP782 microSPECT can detect injury-induced MMP activation in the vessel wall and track the hyperplastic process in vascular remodeling, a technique with clinical promise for tracking the remodeling process in vivo.

Circulation

Quantum Dot Nanosensors and Protease Activity

In an article e-published on October 16 ahead of print in *Analytical Chemistry*, Xia et al. from the Stanford University School of Medicine and the Stanford Nanocharacterization Laboratory (CA) reported on the development of a protease sensing nanoplatform based on semiconductor nanocrystals/quantum dots and on the use of bioluminescence resonance energy transfer (BRET) to detect protease activity in complex biologic samples. The nanosensors function with bioluminescent proteins as the BRET donor, quantum dots as the BRET acceptor, and protease substrates between the 2 as a sensing group. The authors describe the use of an intein-mediated (protein slicing) conjugation strategy for site-specific conjugation of proteins to quantum dots in these nanosensors. A series of quantum dot nanosensors were synthesized for highly sensitive detection of an important class of protease matrix metalloproteinase (MMP) activity. They showed that these nanosensors can detect MMP activity in buffers and in mouse serum with a sensitivity down to a few nanograms per milliliter. The authors also showed the suitability of these nanosensors for multiplex protease assay. The advantages of this approach over fluorescence-based quantum dot nanosensors were reviewed, including small size and enhanced reliability and sensitivity. They concluded that this intein-mediated conjugation method should work with other nanoparticles.

Analytical Chemistry

Real-Time Sensing of Inflammation in Atherosclerosis

Jaffer et al. from the Massachusetts General Hospital Center for Molecular Imaging Research (Boston) reported on October 13 ahead of print in *Circulation* on the development of a near-infrared fluorescence (NIRF) catheter-based strategy for sensing cysteine protease activity during vascular catheterization. The catheter design was based on that of a clinical coronary artery guidewire and was tested in phantom studies and in a rabbit model of atherosclerosis. In rabbits injected with a cysteine protease-activatable NIRF imaging agent, catheter pullbacks through the blood-filled iliac artery detected NIRF signals 24 h later. Saline flush-modulated NIRF signal profiles also distinguished atheromata from normal segments in vivo, and a good correlation was seen between in vivo and ex vivo plaque target-to-background ratios. Histopathologic analyses confirmed strong NIRF signal in plaques, a finding absent in plaques from a control group not injected with the protease agent. In addition, NIRF signals colocalized with immunoreactive macrophages and the cysteine protease cathepsin B. The authors concluded that because their intravascular fluorescence catheter can provide real-time NIRF detection of cysteine protease activity in vessels the size of human coronary arteries, this strategy could aid in the clinical detection of inflammation and high-risk plaques in small arteries.

Circulation

$^{1}H/^{31}P$ MRS Imaging in Carotid Stenosis

Hattingen et al. reported on October 15 ahead of print in *MAGMA* on a study designed to determine whether combined ^{1}H and ^{31}P MR spectroscopic (MRS) imaging before and after treatment of severe internal carotid artery (ICA) stenosis can identify significant changes in energy metabolism in the basal ganglia of both hemispheres. The study included 14 patients with high-grade ICA stenoses and 11 healthy controls, all of whom underwent 2D ^{1}H and 3D ^{31}P MRS imaging before and after treatment. Data elements compared in the 2 groups of subjects and in patients before and after surgery included changes in phosphorylated metabolites, pH, *N*-acetyl-acetate, creatine, and choline-containing compounds. The researchers found that patients had significantly higher adenosindiphosphate (ADP) in basal ganglia ipsi- and contralateral to the side of stenosis than controls. ADP of both hemispheres significantly decreased (~20%) after treatment, as did phosphorylated metabolites. The authors concluded that these results indicate that unilateral high-grade ICA stenosis has an effect on cerebral high-energy metabolism in both hemispheres, an effect that is partially reversible after treatment. This suggests that "the restoration of blood flow in high-grade ICA stenosis recovers the impaired energy balance of the brain."

MAGMA