

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

Low Serum Thyrotropin, Statins, and Hyperthyroidism

In a study e-published on September 18 ahead of print in *Thyroid*, Yandell et al. from the Presbyterian Hospital of Dallas (TX) reported on a study evaluating whether statin use affects the ability of a low serum thyrotropin (TSH) concentration to predict and detect hyperthyroidism. The study included 307 patients (29 taking a statin medication and 278 not taking such medications) with low or undetectable serum TSH concentrations suggestive of hyperthyroidism. Nuclear medicine physicians evaluated radioiodine uptake and scans for all patients. Of the 278 patients not on statins, 234 (84%) had abnormal uptakes and scans, and only 44 (16%) had normal uptakes and scans. Sixteen (55%) of the 29 patients who were on statin medication had normal radioiodine uptakes and scans

despite low serum TSH, and the remaining 13 (45%) had abnormal uptakes and scans, most often showing diffuse thyroid hyperplasia with increased radioiodine uptake. The authors concluded that these results suggest that, "Statins may falsely lower the serum TSH without altering thyroid function ('pseudohyperthyroidism') or, alternatively, statins may improve thyroid function in patients with hyperthyroidism."

Thyroid

Sentinel Node Technique in Thyroid Carcinoma

Raijmakers et al. from the VU University Medical Center (Amsterdam, The Netherlands) reported in the September issue of the *World Journal of Surgery* (2008;32:1961–1967) on a metaanalysis reviewing the diagnostic performance of sentinel node detection for assessment of nodal status in thyroid carcinoma patients and the reported success rates of the blue dye and ^{99m}Tc -colloid techniques. The authors conducted a comprehensive MEDLINE search of studies published through December 2007 with details of sentinel node procedures in patients with thyroid disorders. Fourteen studies, representing 457 patients, met the study criteria. Of these, 10 studies ($n = 329$ patients) used the blue dye technique and 4 ($n = 128$ patients) used the ^{99m}Tc -colloid technique. These techniques had pooled sentinel node detection rates of 83% and 96%, respectively. The authors concluded that the higher rate for ^{99m}Tc -colloid should be considered when choosing optimal sentinel node biopsy approaches in patients with suspected thyroid carcinoma.

World Journal of Surgery

MR vs Scintigraphy for Scaphoid Fracture

In the September issue of the *Journal of Bone and Joint Surgery (British Volume)* (2008;90:1205–1209), Beeres et al. from the Medical Centre

Haaglanden (The Hague, The Netherlands) reported on a study comparing early MR imaging with bone scintigraphy in suspected scaphoid fractures. The study included 100 consecutive patients with suspected scaphoid fracture but no evidence of a fracture on plain radiography. All patients underwent additional MR imaging within 24 h of injury and bone scintigraphy 3–5 d after injury. When both MR imaging and scintigraphy identified a fracture, it was deemed to be truly radiologically occult. When MR and scintigraphy did not agree, clinical and/or radiologic evidence were used to provide a standard for the diagnosis. MR imaging identified 16 scaphoid and 24 other fractures, whereas bone scintigraphy identified 28 scaphoid and 40 other fractures. The reference standard indicated the presence of only 20 scaphoid fractures. MR was false-negative for scaphoid fracture in 4 patients, and bone scintigraphy was false-positive in 8. Sensitivity and specificity were 80% and 100%, respectively, for MR and 100% and 90%, respectively, for bone scintigraphy. The authors concluded that although bone scintigraphy is a highly sensitive and "reasonably specific" investigative tool in this application, the data "did not confirm that early, short-sequence MR imaging was superior to bone scintigraphy for the diagnosis of a suspected scaphoid fracture."

Journal of Bone and Joint Surgery (British Volume)

SPECT and Cardiac Syndrome X

In an article e-published on August 30 ahead of print in the *International Journal of Cardiology*, Fragasso et al. from Università Vita/Salute (Milan, Italy) reported on an investigation of the hypothesis that in cardiac syndrome X patients transient coronary slow flow, as assessed during coronary angiography, may impair myocardial perfusion and thereby affect long-term prognosis. The study included 16 patients with cardiac syndrome X who

showed coronary slow flow during angiography. A total of 34 cardiac syndrome X patients without slow flow served as controls. In patients with slow flow, the phenomenon was consistently worsened by administration of nitrates and reversed by papaverine. Twelve of the slow-flow patients underwent ^{99m}Tc -methoxyisobutylisonitrile SPECT during slow flow. SPECT was repeated first at rest after 2 d and then at peak stress in 9 patients 2 wk later. All 12 patients were found to have a significant perfusion defect in the regions served by the coronary artery that showed slow flow just before tracer injection. After exercise, SPECT showed a perfusion defect in 5 of the 9 patients who underwent stress scanning. At 14 ± 2 y of follow-up, 1 patient with slow flow had died and 4 had developed significant coronary artery disease. All patients in the control group were alive, and none had developed significant cardiac disease. The authors concluded that these results indicate “the slow-flow phenomenon might be the cause of transient myocardial underperfusion in patients with angina and normal coronary arteries.” Because this phenomenon appears to be associated with a poor cardiac prognosis, patients with coronary slow flow should be carefully followed-up.

International Journal of Cardiology

PET in Aortic Valve Stenosis

In the September issue of the *Journal of Cardiovascular Medicine (Hagerstown)* (2008;9:893–898), Carpeggiani et al. from the CNR Institute of Clinical Physiology (Pisa, Italy) reported on a study designed to determine whether impaired myocardial blood flow reserve in severe aortic stenosis is dependent on myocardial hypertrophy and whether the blood flow reserve improves after valve replacement. The study included 15 patients with severe aortic stenosis, normal coronary arteries, and normal left ventricular systolic function (ejection fraction > 50%). Each participant underwent both resting/dipyridamole N-NH₃ flow PET imaging and resting 2D echocardiography before surgery. Eight patients un-

derwent the imaging procedures again after 12 mo. Myocardial blood flow reserve was defined as the dipyridamole/resting mean myocardial blood flow ratio. Results were compared against those from a population of healthy individuals. Patients before surgery had resting myocardial blood flow results that were not significantly different from those in the control group but had lower dipyridamole myocardial blood flow and myocardial blood flow reserve. Before surgery, patients' transvalvular maximal pressure gradient was 86 ± 19 mmHg, valve area was 0.82 ± 0.24 cm, and left ventricular mass index was 185 ± 37 g/m. After surgery, patients' average left ventricular mass index decreased, but no change was seen in resting myocardial blood flow, dipyridamole myocardial blood flow, or myocardial blood flow reserve. No correlation was identified between flow values and pressure gradient or left ventricular mass index, before or after surgery. The authors concluded that these data suggest that myocardial blood flow reserve in severe aortic stenosis is depressed independently of myocardial hypertrophy and transvalvular pressure gradient and that, for this reason, “removal of pressure overload by valve replacement is not able to improve myocardial perfusion.”

Journal of Cardiovascular Medicine (Hagerstown)

Radioguided Occult Breast Lesion Localization

In an article e-published on September 2 ahead of print in the *Journal of Surgical Oncology*, Van Esser et al. from the University Medical Centre Utrecht (The Netherlands) reported on radioguided occult lesion localization (ROLL) as a promising alternative to wire-guided localization for nonpalpable invasive breast cancer. The study included 40 patients with 41 invasive breast carcinomas. Patients received intratumoral ^{99m}Tc -nanocolloid injections of either 120 MBq on the day of surgery or 370 MBq 1 d before surgery. At surgery, the sentinel node was located using patent blue and a γ probe, which was also used to guide tumor

excision. Sentinel nodes were found and removed in 35 (88%) of the 40 patients. Invasive tumors were adequately excised in 31 (78%) of the 40 patients. Carcinomas in situ in 2 patients (5%) were inadequately excised, and both the invasive and in situ tumors in 3 patients were inadequately excised. The authors concluded that “the ROLL procedure seems to be an alternative to wire-guided localization in patients with nonpalpable breast carcinoma” and called for a randomized clinical trial to validate these results.

Journal of Surgical Oncology

Seasonal Variations in Serotonin Binding

Molecular imaging and assessment are providing novel insights into many aspects of the human condition that have long been accepted as givens—such as the association of bright and sunny days with happiness and energy. In an article in the September issue of the *Archives of General Psychiatry* (2008;65:1072–1078), Praszak-Reider et al. from the University of Toronto reported on a study of the relationship between seasonal variation in serotonin transport binding in humans and daily duration of sunshine. The study included 88 drug-naïve healthy individuals in whom regional serotonin transporter binding potential values were assessed over a 4-y period by ^{11}C -3-amino-4-(2-dimethylamino-methyl-phenylsulfanyl) benzonitrile PET. Results were compared with meteorologic data. The authors found that serotonin transporter binding potential values were significantly higher in all brain regions in individuals in the fall and winter than in the spring and summer. Binding potential values showed negative correlations with the average duration of daily sunshine in all brain regions, so that higher values coincided with times of lesser light. These results reinforced previous evidence in the literature that serotonin transporter binding potential values vary seasonally and point to previously undescribed physiologic mechanisms with the potential to explain seasonal

changes in normal and pathologic behaviors.

Another perspective was provided by Koskela et al. from Helsinki University Central Hospital (Finland) in the September issue of *Chronobiology International* (2008;25:657–665). This group used ^{123}I -ADAM SPECT to investigate within-subject seasonal variation in brain serotonin transporter binding in 12 healthy individuals. They found no systematic variation in the midbrain or thalamus between images acquired in the summer and winter. These authors concluded that these data suggest that, “factors other than season are more important in causing within-subject variation of brain serotonin transporter binding between summer and winter.”

Archives of General Psychiatry
Chronobiology International

THERAPY

^{90}Y Radioembolization for Neuroendocrine Liver Metastases

King et al. from the University of New South Wales (Sydney, Australia) reported in the September 1 issue of *Cancer* (2008;113:921–929) on the safety and efficacy of radioembolization with ^{90}Y microspheres in patients with inoperable neuroendocrine liver metastases. The study included 34 such patients (22 men, 12 women; mean age, 61 y, range, 32–79 y). Patients were administered ^{90}Y -resin microspheres (selective internal radiation spheres) through a temporarily placed percutaneous hepatic artery catheter along with a 7-d systemic infusion of 5-fluorouracil. Patients were monitored for 35.2 ± 3.2 mo after treatment, and serum markers and tumor size assessed by CT were used to evaluate treatment response. The primary neuroendocrine tumor site was the bronchus in 1 patient, the medullary thyroid in 2 patients, gastrointestinal in 15 patients, pancreas in 8 patients, and unknown in 8 patients. Tumors were classified as vipoma ($n = 1$), somatostatinoma ($n = 1$), glucagonoma ($n = 2$), large cell ($n = 3$),

carcinoid ($n = 25$), and of unknown origin ($n = 2$). Adverse effects associated with radioembolization included abdominal pain, nausea, fever, and lethargy. Two patients developed biopsy-proven radiation gastritis, 1 patient developed a duodenal ulcer, and 1 early death resulted from liver dysfunction and pneumonia. Mean overall survival was 29.4 ± 3.4 mo. Symptomatic responses were noted in 18 (55%) of 33 patients at 3 mo and in 16 (50%) of 32 patients at 6 mo. Liver responses were observed on CT in 50% of patients, including 6 (18%) with complete responses and 11 (32%) with partial responses. The authors concluded that these results suggest that “radioembolization with ^{90}Y -resin microspheres can achieve relatively long-term responses in some patients with nonresectable neuroendocrine liver metastases.”

Cancer

RIT and Primary Cutaneous B-Cell Lymphomas

In an article published in the September issue of *Leukemia and Lymphoma* (2008;49:1702–1709), Maza et al. from the Charite-Universitätsmedizin Berlin (Germany) added to the growing numbers of reports on ^{90}Y -ibritumomab tiuxetan radioimmunotherapy effectiveness. They reported on the results of a pilot study to evaluate the outcome and assess complications of ^{90}Y -ibritumomab tiuxetan therapy in patients with primary cutaneous B-cell lymphomas. The study included 10 patients with relapsed primary cutaneous B-cell lymphomas who were treated with rituximab on d 1 and 8, followed by a single dose of ^{90}Y -ibritumomab tiuxetan. The overall response rate was 100%, and the complete response rate was 100%, with a median time to relapse of 12 mo. Ongoing remission was achieved in 4 patients (median follow-up, 19 mo). The most frequent complication was transient and reversible myelosuppression (grades 3–4). The authors concluded that “radioimmunotherapy with ^{90}Y -ibritumomab tiuxetan is an effective treatment in relapsed primary cutaneous follicle centre lymphomas and diffuse large B-cell lymphoma” and called for controlled

randomized trials to extend these investigations.

Leukemia and Lymphoma

MOLECULAR IMAGING

Imaging Stem Cell-Mediated Bone Healing

In an article e-published on August 27 ahead of print in the *Journal of Orthopaedic Research*, Lee et al. from the Stanford University School of Medicine (CA) reported on a study using molecular imaging technologies to validate the in vivo life cycle of adipose-derived multipotent cells (ADMCs) in an animal model of skeletal injury. Primary ADMCs were transfected with a fusion reporter gene and injected intravenously into mice with bone injury or after sham operation. A group of control injured animals was not transfected. Several imaging techniques were used to monitor stem cell migration and effects, including bioluminescence imaging, ^{18}F -fluorohydroxymethylbutyl-guanine small animal PET, ^{18}F -fluoride ion small animal PET, and small animal CT. Bioluminescence microscopy and immunohistochemistry were also performed. ADMC movement from the lungs to the injury site was verified by bioluminescence imaging. Microscopy and immunohistochemistry confirmed the presence of ADMCs in bone defects. CT results indicated more bone healing in the cell-injected group than in the noninjected group at 7 d after injury/surgery. The authors concluded that these results suggest that “molecular imaging technologies can validate the usage of adult adipose tissue-derived multipotent cells to promote fracture healing” and that imaging shows promise for utility in establishing therapeutic strategies, including dosage and administration route.

Journal of Orthopaedic Research

Bone Sialoprotein and Bone Metastasis

Tu et al. from the Tufts University School of Dental Medicine (Boston, MA) reported on August 28 ahead of print in the *Journal of Cell Physiology*

on a study designed to explore the role of bone sialoprotein overexpression in osteolytic metastasis. The research focused on 4T1 murine breast cancer cells in 2 transgenic mouse models in which bone sialoprotein expression was elevated. In 1 model, this elevation was in all tissues (CMV-BSP mice), and in the other the elevation was only in osteoclasts (CtpsK-BSP mice). The authors found that systemic metastasis of the cancer cells was significantly increased in the CMV-BSP mice, whereas the targeted bone sialoprotein overexpression in osteoclasts in the CtpsK-BSP mice resulted in osteoclastogenesis and activated specific osteoclastic differentiation markers. Mice underwent both small animal CT and in vivo optical imaging. CT showed that trabecular bone volume and bone mineral density were reduced in the CtpsK/BSP mice. Real-time optical imaging indicated that targeted bone sialoprotein overexpression in osteoclasts promoted bone metastasis of breast cancer cells. These and additional imaging procedures and staining led the authors to conclude that “host tissue-derived bone sialoprotein also plays important roles in breast cancer metastasis through inducing tumor cell seeding into the remote host tissues” and that “osteoclast-derived bone sialoprotein promotes osteoclast differentiation in an autocrine manner and consequently promotes osteolytic bone metastasis of breast cancer.”

Journal of Cell Physiology

Imaging Adipose Tissue Regain Mechanisms

Birsoy et al. from the Rockefeller University (New York, NY) reported in the September 2 issue of the *Proceedings of the National Academy of Sciences of the United States of America* (2008;105:12985–12990) on the creation of a transgenic mouse with leptin expression characteristics that facilitate in vivo imaging of the cellular

program responsible for the restoration of adipose tissue mass after weight loss. The mouse model expressed the luciferase reporter gene under the control of leptin regulatory sequences, facilitating noninvasive imaging of leptin expression. The authors found that fasting or leptin treatment resulted in retention of lipid-depleted adipocytes in adipose depots. In additional studies, a leptin withdrawal protocol was used to induce a state of acute leptin deficiency in wild type mice. In these mice, imaging showed transient deposition of large amounts of glycogen within preexisting, lipid-depleted adipocytes, followed by rapid reaccumulation of lipid. This cellular response was found to be associated with induction of mRNAs for the entire pathway of enzymes necessary to convert glucose into the acetyl-CoA molecule and glycerol, key substrates for the synthesis of triglycerides.

Proceedings of the National Academy of Sciences USA

Novel mAb for IGF-I Receptor-Dependent Tumors

Shang et al. from Genetech, Inc. (South San Francisco, CA), reported in the September issue of *Molecular Cancer Therapeutics* (2008;7:2599–2608) on the development of a humanized, affinity-matured anti-human insulin-like growth factor-I receptor (IGF-IR) monoclonal antibody (h10H5) that binds with high affinity and specificity to the cellular domain. They described in vitro studies in which h10H5 showed antiproliferative effects on several cancer cell lines. In in vivo studies, h10H5 showed single-agent antitumor efficacy in human SK-N-AS neuroblastoma and SW527 breast cancer xenograft models. This efficacy was enhanced in combination with docetaxel or with an antivascular endothelial growth factor antibody. Additional investigation showed that the antitumor activity of

h10H5 was associated with decreased protein kinase gene AKT activation and glucose uptake, as well as significant changes involving DNA metabolic and cell cycle machineries. The authors concluded that “these data support the clinical testing of h10H5 as a biotherapeutic for IGF-IR-dependent human tumors and furthermore illustrate a new method of monitoring its activity noninvasively in vivo” via ^{18}F -FDG PET.

Molecular Cancer Therapeutics

PET and Targeted Viral Envelopes

Flexman et al. from the University of Washington (Seattle) reported in the September issue of *IEEE Transactions on Nanobioscience* (2008;7:223–232) on a PET investigation of the initial biodistribution of magnetically targeted viral envelopes in a rat model, an approach designed to facilitate organ-specific gene and drug therapy. The group had previously described its technique for tracking viral envelopes with PET (*Conference Proceedings IEEE Engineering in Medicine and Biology Society*. 2005;6:5691–5694). The viral envelopes encapsulated iron oxide nanoparticles and ^{18}F -fluoride and were injected intravenously into rats. Control rats received injections of encapsulated materials alone. Magnets were permanently fixed on the heads of the rats during scanning. PET results and subsequent histology indicated that the envelopes accumulated in the liver and spleen and that the activity in these areas remained higher in animals injected with the envelopes than in control groups. Magnetic force was also found to significantly alter the biodistribution of the viral envelopes to a target structure. The authors concluded that this could “enable region-specific delivery of therapeutic vehicles noninvasively,” a process that could be monitored quantitatively by PET.

IEEE Transactions on Nanobioscience