



Each month the editor of *Newsline* selects article on diagnostic, therapeutic, research, and practice issues from a range of international publications. Many selections come from outside the standard canon of nuclear medicine and radiology journals. This month the literature contained a remarkable number of articles on the utility of PET and other nuclear medicine techniques in assessment of orthopedic conditions and treatments. Several of these are included in this review. Note that although we have divided the articles into diagnostic and therapeutic categories, these lines are increasingly blurred as nuclear medicine capabilities 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.

Diagnosis

¹⁸F-Fluoride PET and Fatigue-Induced Bone Damage

In an article e-published on March 10 ahead of print in *Bone*, Silva et al. from the Washington University School of Medicine (St. Louis, MO) reported on the use of ¹⁸F-fluoride PET to describe the time course of bone response to fatigue. The study involved inducing fatigue (at 30%, 45%, 65%, or 85% of fracture displacement) in 1 forelimb of adult rats. The other forelimb in each rat served as the control. Rats were imaged with ¹⁸F-fluoride and small animal PET at 4 hours and at 2, 4, 7, 9, 11, 18, 24, and 30 days after the fatigue event. Significant increases in tracer uptake were found in the fatigued forelimbs on the

first day and reached peak levels 4–9 days later. The level of uptake was significantly related to the level of fatigue displacement. On the basis of these results and accompanying histologic findings, the authors concluded that “a single bout of fatigue loading leads to a transient increase in the uptake of ¹⁸F-fluoride, that the uptake is in proportion to the level of initial damage and is associated with increased vascularity and woven bone formation in the first week after loading.”

Bone

¹⁸F-FDG PET and Skeletal Blood Flow in Exercise

Kalliokoski et al. from the Bispebjerg Hospital (Copenhagen, Denmark) reported on March 23 ahead of print in the *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology* on an ¹⁸F-FDG PET study designed to elucidate the role of nitric oxide and prostaglandins in local skeletal muscle blood flow during exercise. The study included 7 healthy young men who underwent near infrared spectroscopy and ¹⁸F-FDG PET imaging with and without local blockade of nitric oxide and prostaglandins (by L-NAME and indomethacin infusion directly into muscle) at rest and during dynamic knee-extension exercise. Blood flow and tracer uptake were measured. The results indicated that local blockade during exercise decreased blood flow only locally. Muscle glucose uptake showed no differences in response to the blockade. The authors noted that these results suggest that nitrous oxide and prostaglandins in healthy young men “synergistically contribute to the local regulation of blood flow in skeletal muscle independently of muscle glucose uptake.” The vasodilators can play a role in regulating microvascular blood flow in localized regions of muscle without influencing regional

glucose uptake. The implied conclusion was that “local substrate uptake in skeletal muscle can be regulated independently of regional changes in blood flow.”

American Journal of Physiology: Regulatory, Integrative and Comparative Physiology

¹⁸F-FDG PET in Prosthetic Loosening Assessment

In the March 3 issue of *BMC Musculoskeletal Disorders* (2006;7:20), Delank et al. from Cologne University (Germany) reported on a study of the clinical value of ¹⁸F-FDG PET in preoperative assessment of inflammation and loosening in hip and knee joint prostheses. The study included 27 patients who were scheduled for surgical procedures to correct prosthetic loosening. Each patient underwent ¹⁸F-FDG PET imaging and multiphase bone scintigraphy (27 hips and knees plus 9 additional intact prosthetic joints within the PET field of view). Imaging findings were compared with results from surgery, histopathology, and microbiology. PET and bone scintigraphy were approximately equal in their abilities to correctly identify loosening (76.4% and 75% of cases, respectively). PET was 100% sensitive for septic cases and 45.5% sensitive in cases of increased abrasion and aseptic foreign-body reactions. PET was not able to reliably distinguish between abrasion-induced and bacterial-caused inflammation. The authors concluded that ¹⁸F-FDG PET provides a highly accurate prediction of periprosthetic septic inflammatory tissue, so that “a negative PET result in the setting of a diagnostically unclear situation eliminates the need for revision surgery.” However, they cautioned that a positive PET result cannot provide reliable information on the cause of inflammation.

BMC Musculoskeletal Disorders

Specialty Bias in Interpretation of Orthopedic Images

In an article published in the March/April issue of *Spine Journal* (2006;6:177–184), Mulconrey and colleagues from the University of Nebraska Medical Center (Omaha) reported on the effect of subspecialty bias on the interpretation of various imaging modalities in the assessment of patients with complaints of low back or leg pain. The retrospective review included a random selection of 17 patients who presented to an orthopedic spine specialist with complaints of mechanical low back or leg pain. Each had undergone a thorough clinical workup, including MR imaging, bone scans, and SPECT. A team of orthopedists and radiologists interpreted the studies and responded to a multi-item questionnaire about the findings. The results were compared with a “group consensus.” Interobserver reliability between the 2 groups of specialists was high for identification of a degenerative disc, spondylolisthesis, and Modic change ($\kappa = 0.773, 0.728, \text{ and } 0.669$, respectively). The level of agreement was lower for bone scintigraphy and SPECT ($\kappa = 0.539 \text{ and } 0.460$, respectively). Averaged reviewer-predicted bone scan results showed a positive predictive value of 68% and a negative predictive value of 84%. SPECT results were similar (positive predictive value of 66%, negative predictive value of 84%), although SPECT identified 24% more lesions in the lumbar spine than did the bone scan. The ability to interpret MR scans of the lumbar spine was comparable between the specialties. The authors concluded that, “the presence of MRI changes enables an accurate prediction of bone scan or SPECT scan findings” and that the SPECT scan “demonstrates an increased sensitivity in the detection of spinal abnormalities and the ability to localize a lesion when compared with planar bone scan.”

Spine Journal

Comparison of Imaging Techniques in Prosthetic Loosening

Temmerman et al. from the VU Medical Centre (Amsterdam, The Netherlands) reported on March 18 ahead of print in the *Archives of Orthopaedic and Trauma Surgery* on a study comparing the relative utility of plain radiography, subtraction arthrography, nuclear arthrography, and bone scintigraphy in identifying aseptic femoral component loosening. The retrospective study assessed the diagnostic accuracy and interobserver reliability of these techniques in 78 patients referred for evaluation of femoral hip prostheses using all 4 of the imaging modalities. Results were compared with findings on surgery or over clinical follow-up. The sensitivity and specificity of plain radiography, subtraction arthrography, nuclear arthrography, and bone scintigraphy (81% and 74%, 47% and 78%, 69% and 76%, and 88% and 50%, respectively) were recorded. Considerable interobserver variability was found in the results. Among the authors’ conclusions was that “bone scintigraphy and nuclear arthrography together made a significant contribution to the diagnosis when used in combination with plain radiography and are, when plain radiography is inconclusive, useful additional diagnostic techniques for the detection of femoral component loosening.”

Archives of Orthopaedic and Trauma Surgery

PET Looks at Muscle EMG and Perfusion in the Knee

Laaksonen et al. from the University of Turku (Finland) reported in the March issue of *Clinical Physiology and Functional Imaging* (2006;26:99–105) on a PET study designed to investigate the association between muscle blood flow and electromyographic (EMG) activity in different compartments of the quadriceps femoris (QF) muscle. The study included 12 healthy male participants,

who were imaged with ^{15}O -water PET during 2 submaximal exercise sessions of different intensities. Force of knee extensors and muscle EMG activity in the vastus lateralis (VL), vastus medialis (VM), and rectus femoris (RF) muscles were also recorded. The exercise intensity and average force production were higher during the second exercise session than the first, but average EMG activity was slightly lower or unchanged. PET indicated that perfusion was unchanged in the second exercise period when measured over the entire QF muscle. However, individual changes in muscle perfusion were closely correlated to changes in muscle EMG activity in the VL and VM, but poorly correlated in the RF muscle. The authors concluded that “the different associations between muscle perfusion and EMG activity in different QF muscles suggest a specific functional role of the vasti muscles and the RF muscle.”

Clinical Physiology and Functional Imaging

Leptin Plasma Levels in Obese Patients

Schindler et al. from the University of California at Los Angeles reported in the March 21 issue of the *Journal of the American College of Cardiology* (2006;47:1188–1195) on a study using ^{13}N -ammonia PET to evaluate the effects of obesity, insulin resistance, and inflammation on coronary circulatory function and to look at the relationship between these results and leptin levels. The study included 72 patients divided into 3 groups based on body mass index (BMI): controls ($20 \leq \text{BMI} < 25$), overweight ($25 \leq \text{BMI} \leq 30$), and obese ($\text{BMI} > 30$) individuals. Each patient underwent assessment of myocardial blood flow (MBF) response by cold pressor test and ^{13}N -ammonia PET imaging to measure pharmacologic vasodilation. BMI was found to be significantly correlated to the Homeostasis Model Assessment Index of insulin resistance and C-reactive protein levels. The cold

pressor test indicated that endothelium-related change in MBF declined progressively in overweight and obese groups, and dipyridamole-induced total vasodilator capacity was significantly lower in obese than in control individuals. Only in the obese group was leptin plasma level significantly correlated with endothelium-related change in MBF. These results indicated that “increased body weight is independently associated with abnormal coronary circulatory function that progresses from an impairment in endothelium-related coronary vasomotion in overweight individuals to an impairment of the total vasodilator capacity in obese individuals.” The authors also noted that additional research should be directed to explore whether elevated leptin plasma levels in patients who are obese might exert beneficial effects on the coronary endothelium to counterbalance the adverse effects of increases in body weight on coronary circulatory function.

Journal of the American College of Cardiology

PET and Lung Inflammation in Cystic Fibrosis

Chen et al. from the Washington University School of Medicine (St. Louis, MO) reported ahead of print on March 16 in the *American Journal of Respiratory and Critical Care Medicine* on a study designed to determine whether ^{18}F -FDG PET can be used as a noninvasive method to quantify lung inflammation in patients with cystic fibrosis (CF). The study included 20 patients with CF and 7 healthy volunteers, each of whom underwent PET imaging. A subset of 7 volunteer patients also underwent bronchoalveolar lavage. Patients were grouped by rate of pulmonary function decline as stable, intermediate, or rapidly declining. Tracer uptake (net influx rate constant) was significantly elevated in the CV patients when compared with healthy volunteers and most elevated in the group with rapidly declining pulmonary function. Tracer uptake also correlated positively with the

number of neutrophils present in lavage fluid. The authors concluded that not only can ^{18}F -FDG PET be used to assess inflammatory burden in patients with CF, but the elevations in tracer uptake “may be able to identify patients with more aggressive disease and may be useful in monitoring changes in inflammatory burden in response to novel treatments.”

American Journal of Respiratory and Critical Care Medicine

Elevated Splenic SUVs in PET Imaging of Malaria

Kawai and colleagues representing a group of medical schools and imaging centers in Japan reported in the March issue of the *American Journal of Tropical Medicine and Hygiene* (2006;74:353–360) on a study correlating the results of ^{18}F -FDG PET imaging with pathology changes observed in a primate model of severe human malaria. The researchers performed whole-body PET imaging in *Plasmodium coatneyi*-infected Japanese macaques in the acute phase of disease development. The imaging results showed increased splenic tracer uptake, indicating marked enhancement of glucose metabolism. Standardized uptake values for the spleen were significantly higher in infected monkeys than in controls. Subsequent pathology indicated splenomegaly in all infected monkeys, hyperplasia of lymphoid follicles in white pulp, a large number of activated macrophages, and congestion of parasitized red blood cells and malaria pigments in red pulp. The authors concluded that an “increase in splenic glucose uptake may thus be closely related to activation of the splenic clearance system against blood-stage malarial parasites.”

American Journal of Tropical Medicine and Hygiene

PET and Preclinical AD Markers in CSF

In the March issue of the *Annals of Neurology* (2006;59:512–519), Fagan

et al. from the Washington University School of Medicine (St. Louis) reported on a study to determine whether the mean decrease observed in cerebrospinal fluid (CSF) amyloid- β (42) in dementia of the Alzheimer’s type may reflect plaques acting as “sinks,” hindering transport of amyloid- β (42) between brain and CSF. Pittsburgh Compound B (PIB) PET imaging was used to characterize the brain amyloid load, and these results were then compared with CSF amyloid- β (42) and other measures in a group of 24 clinically characterized research subjects. The results divided the participants into 2 clearly distinguished groups: those with positive PIB binding and lowest CSF amyloid- β (42) levels, and those with negative PIB binding and the highest CSF amyloid- β (42) level. PIB binding did not correlate with other measures, including CSF amyloid- β (40) tau, phospho-tau(181), plasma amyloid- β (40), or plasma amyloid- β (42). The most intriguing finding was that PIB binding and low CSF amyloid- β (42) did not correspond with clinical diagnoses in all patients. Three individuals who were assessed as cognitively normal were PIB-positive with low CSF amyloid- β (42), which the authors noted as evidence of preclinical Alzheimer’s disease (AD). They concluded that the results “suggest that brain amyloid deposition results in low CSF amyloid- β (42), and that amyloid imaging and CSF amyloid- β (42) may potentially serve as antecedent biomarkers of (preclinical) AD.”

Annals of Neurology

SPECT and Frontotemporal Dementia

McMurtray et al. from the University of California at Los Angeles reported in the February 28 issue of *Neurology* (2006;66:517–522) on a study characterizing the presenting clinical features of frontotemporal dementia (FTD) and contrasting these with the degree of frontal and temporal hypoperfusion on SPECT imaging.

The investigation included 74 patients who were first evaluated with neurologic work-ups and SPECT and either met the criteria for the FTD form of frontotemporal lobar degeneration (excluding primary progressive aphasia and semantic dementia) at initial evaluation (25 patients) or progressed to meet these criteria during a 2-year follow-up period (49 patients). Initial neurologic features were compared with observed variations in regional SPECT hypoperfusion. Patients with FTD were found to have more hypoperfusion in the right frontal lobe than in other regions, with those so diagnosed at initial evaluation having the highest degree of right frontal hypoperfusion. Right frontal lobe involvement was associated with apathy and could predict loss of insight, environmental dependency, and stereotyped behaviors. Left frontal hypoperfusion was associated with a decline in personal hygiene, and left temporal hypoperfusion with compulsions and mental rigidity. The authors concluded that FTD at initial presentation is “disproportionately a right frontal disease evident on behavioral measures and on SPECT,” but added that patients with FTD can also present initially with other regional differences in clinical diagnostic features.

Neurology

¹⁸F-FDG PET and Traumatic Diffuse Brain Injury

In an article e-published on March 20 ahead of print in the *Journal of Neurology, Neurosurgery, and Psychiatry*, Nakayama et al. from the Kizawa Memorial Hospital (Japan) reported on an ¹⁸F-FDG PET study using statistical parametric mapping (SPM) analysis to investigate the cerebral metabolism of chronic-stage patients with traumatic diffuse brain injury (TDBI). The study included 52 patients with TDBI without large focal lesions, who were divided into 3 groups based on consciousness or cognitive function: (A) patients in a state with higher brain dysfunction (22); (B) patients in a minimally

conscious state; and (C) patients in a vegetative state (17). Patterns of regional cerebral metabolism for each individual were assessed with PET and compared on SPMs with those of healthy volunteers. Hypometabolism was noted in the patient group bilaterally in the medial prefrontal regions, the medial frontobasal regions, the cingulate gyrus, and the thalamus. Hypometabolism was greatest in group C. The authors concluded that these results suggest that bilateral hypometabolism in the areas noted may “reflect the clinical deterioration of TDBI, which is due to functional and structural disconnections of neural networks rather than to direct cerebral focal contusion.”

Journal of Neurology, Neurosurgery, and Psychiatry

Long-Term Follow-Up on Radiation Release

Several studies appeared in the medical literature in March reporting on continued assessments of medical sequelae to radiation-release events, including the 1986 accident at Chernobyl and the World War II bombing of Japanese cities. Ivanov et al. from the Russian Academy of Medical Sciences (Obninsk, Russia) reported on March 17 ahead of publication in *Radiation and Environmental Biophysics* on thyroid cancer incidence among children and adolescents in the Bryansk oblast area in the 1991–2001 follow-up period. Statistical analyses showed significant radiation risk only for those exposed as children between the ages of 0 and 9 years. For girls whose age at exposure was 0–4 years, the excess relative risk per 1 Gy for the study period was 45.3 (with internal control) and 28.8 (with external control). The corresponding figures for boys whose age at exposure was 0–9 years were 68.6 and 177.4. Jacob et al. from the GSF-Institute of Radiation Production (Neuherberg, Germany) reported in the March issue of the *Journal of Radiological Protection* (2006;25:51–67) on a similar statistical study among Ukrainians and

Belarusians who were children or adolescents at the time of the Chernobyl release. The authors identified a baseline of thyroid cancer incidence in these regions and correlated these data with location, gender, and age. They determined that the baseline cases contributed about 70% to the thyroid cancer incidence in Ukraine and about 40% to the incidence in Belarus. Tondel et al. from Linköping University (Sweden) reported in the March issue of the *American Journal of Industrial Medicine* (2006;49:159–168) on the increased incidence of malignancies in individuals across a wide age spectrum after the fallout of ¹³⁷Cs over Sweden after the Chernobyl accident in 1986. The study included 1,137,106 inhabitants who were 0–60 years old in 1986 and lived in 8 counties of Sweden with the highest levels of radioactive fallout. Using sophisticated maps and satellite technology, each individual was ranked for exposure to ¹³⁷Cs. The authors identified an average excess relative risk per 100 nGy/hour of 0.042, with the possibility of additional levels of risk for thyroid cancer and leukemia.

In a study published on March 1 in the *Journal of the American Medical Association* (2006;295:1060–1062), Imaizumi et al. from the Radiation Effects Research Foundation (Nagasaki, Japan) evaluated the prevalence of thyroid diseases and radiation-dose responses in atomic bomb survivors. The survey study included 4,091 individuals. Thyroid diseases were identified in 1,833 (44.8%) of the total participants. In the subgroup of 3,185 participants (which excluded individuals exposed in utero, who were out the city at the time of the atomic bombings, or who experienced unknown radiation doses), the incidences of all solid nodules, malignant tumors, benign nodules, and cysts were 14.6%, 2.2%, 4.9%, and 7.7%, respectively. The prevalence of positive thyroid antibodies, antithyroid antibody-positive hypothyroidism, and Graves disease was 28.2%, 3.2%, and 1.2%, respectively, in this same group. The authors estimated that about 28% of

all solid nodules, 37% of malignant tumors, 31% of benign nodules, and 25% of cysts in the overall group were associated with radiation exposure at a mean and median thyroid radiation dose of 0.449 Sv and 0.087 Sv, respectively. They concluded that “a significant linear radiation dose response for thyroid nodules, including malignant tumors and benign nodules, exists in atomic bomb survivors,” but added that no significant dose response is apparent for autoimmune thyroid diseases.

*Radiation and Environmental
Biophysics*

Journal of Radiological Protection

*American Journal of
Industrial Medicine*

*Journal of the American
Medical Association*

Therapy

Pretargeted RIT in Thyroid Carcinoma

In an article e-published ahead of print on March 20 in the *Journal of Clinical Oncology*, Chatal and colleagues from France and the United

States reported on a study of the efficacy of pretargeted radioimmunotherapy (RIT) with a bispecific monoclonal antibody (BsmAb) and a radiolabeled bivalent hapten in patients with metastatic medullary thyroid carcinoma (MTC). The study included 29 patients with advanced, progressive MTC, who received an anticarcinoembryonic antigen (CEA)/antidiethylenetriamine pentaacetic acid indium BsmAb, followed 4 days later by a ¹³¹I-labeled bivalent hapten. The authors looked at overall survival in this group and a group of 39 patients with MTC who were not treated. They found that the overall survival was significantly longer in high-risk, treated patients than in high-risk, untreated patients. Patients defined as biologic responders (47% of those treated) experienced significantly longer survival than either nonresponders or untreated patients. Treated patients with bone/bone-marrow disease had longer survival times than patients without such involvement. These and accompanying laboratory findings led the authors to conclude that short serum calcitonin doubling times and bone-marrow involvement appear to be prognostic

indicators in MTC patients who undergo pretargeted RIT.

Journal of Clinical Oncology

Measles Virus Therapy in Ovarian Cancer

Hasegawa et al. from the Mayo Clinic College of Medicine (Rochester, MN) reported in the March 15 issue of *Clinical Cancer Research* (2006;12:1868–1875) on a virotherapy study with 2 oncolytic measles viruses: MV-CEA, which is being tested in patients with ovarian cancer and which can be monitored by measuring blood carcinoembryonic antigen (CEA) levels; and MV-NIS, which codes for the thyroidal sodium iodide symporter (NIS) and can be monitored by serial radioiodine imaging. The authors performed combined therapy in a mouse model of ovarian cancer and determined that not only is the dual therapy with MV-CEA and MV-NIS superior to treatment with either virus alone, but it “allows noninvasive monitoring of virotherapy via soluble marker peptide and gamma camera imaging.” They pointed to the important implications for the clinical development of oncolytic measles viruses.

Clinical Cancer Research

(Continued from page 15N)

Hospital (MGH), and attending interventional radiologist at MGH. He is also a member of the Dana Farber Harvard Cancer Center, the Broad Institute (Chemical Biology Program), and the Harvard Stem Cell Institute (HSCI), leading its imaging program. His research interests include the development of novel molecular imaging techniques, tools for early detection of cancer, and development of nanomaterials for sensing. He has published more than 400 articles in peer-reviewed journals, has authored and coauthored several textbooks, and holds 15 patents. He is a founding member of the Society for Molecular Imaging and served as its president in 2002. His work has been honored with numerous awards, including the J. Taylor International Prize in Medicine, the Millennium Pharmaceuticals Innovator Award, the Association of University Radiologists Memorial Award, the American Roentgen Ray Society President's Award, and the Society for Molecular Imaging (SMI) Lifetime Achievement Award.

Individuals named as authors of top abstracts for presentations at the meeting included SNM member Werner Langsteger, MD, for “Fluor Choline (FCH) PET/CT in Preoperative Staging and Follow up of Prostate Cancer,” Dnyanesh Tipre, PhD, for “Cardiac and Extra-Cardiac Sympathetic Denervation in Parkinson Disease with Orthostatic Hypotension and in Pure Autonomic Failure”; SNM member Marc S. Berridge, PhD, for “Biodistribution of Smoked Nicotine as Measured by PET”; Jacob Y. Hesterman, for “Design and Evaluation of a Novel, High-Resolution Small-Animal SPECT System”; and Parasuraman Padmanabhan, MD, for “Simultaneous Non-Invasive Imaging of Estrogen Receptor Ligand Induced Homodimerization and Gene Transactivation in Living Mice.” Tipre, Hesterman, and Padmanabhan were also recognized for their contributions as young investigators.

Academy of Molecular Imaging