Each month the editor of Newsline selects article on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. Note that although we have divided the articles into diagnostic and therapeutic categories, these lines are increasingly blurred as nuclear medicine capabilities rapidly expand. Many diagnostic capabilities are now enlisted in direct support of and, often, in real-time conjunction with therapies. This month, a number of briefs are related to both new and refined applications in nuclear cardiology. 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

PET and Effects of Prenatal Alcohol Exposure

In the September issue of *Alcoholism, Clinical and Experimental Research* (2005;29:1684–1697), Schneider et al. from the University of Wisconsin–Madison, the University of California–Irvine, and the University of Manchester (England), reported on a study using ^{18}F-fallypride and 6-^{18}F-fluoro-*m*-tyrosine PET to assess the effects of moderate prenatal alcohol exposure in an animal model. The study included 35 young adult rhesus monkeys who represented the offspring of 4 groups of females: (1) a group that consumed moderate amounts of alcohol during the first 50 days of gestation; (2) a group that consumed moderate amounts of alcohol during middle-to-late gestation; (3) a group that consumed moderate amounts of alcohol throughout gestation; and (4) a control group that consumed an isocaloric solution in corresponding gestational periods. Each young adult offspring underwent separate PET imaging for trapping of ^{18}F-fallypride and 6-^{18}F-fluoro-*m*-tyrosine to assess the ratio of striatal dopamine D2 receptor binding to dopamine synthesis. Alcohol exposure during early gestation and continuous exposure throughout gestation reduced this ratio, whereas middle-to-late alcohol gestation exposure increased the ratio. The authors concluded that these results indicate that the vulnerability of the dopamine system to the effects of moderate doses of alcohol during gestation depends on the timing of alcohol exposure, with early exposure resulting in a reduction of dopaminergic function in adulthood and middle-to-late exposure (without early exposure) elevating dopaminergic function. They added that, "Continuously exposed monkeys showed the largest effect, suggesting that the sooner women stop drinking, the better it is for the fetus."

Alcoholism, Clinical and Experimental Research

Tendon Glucose Uptake in Exercise

Hannukainen et al. from the University of Turku (Finland) reported in the November issue of the *International Journal of Sports Medicine* (2005;26:727–731) on the use of PET to measure and compare tendon and muscle glucose uptake during exercise of varying intensities. The study included 8 young adults, each of whom underwent ^{18}F-FDG PET imaging on 3 separate days. Exercise consisted of stationary cycling for 35 minutes at 30%, 55%, and 75% of maximal O_2 uptake on days 1, 2, and 3, respectively. On each day, the tracer was injected after 10 minutes of exercise, and exercise was then continued for an additional 25 minutes before PET scanning from the thigh to ankle. The authors found that glucose uptake in the Achilles tendon remained essentially unchanged before and after exercise and during exercise of varying intensities, whereas glucose uptake in thigh muscles increased significantly, both after exercise and in amounts directly related to the intensity of exercise. The authors noted that these findings might be somewhat limited by the ergonomics of cycling, which demand more exertion from the thighs than from the Achilles tendon, but added that studies such as these point to a wide range of promising research with PET in sports medicine.

International Journal of Sports Medicine

Hyperparathyroidism and the Hanford Nuclear Site

In an article e-published on October 4 in the *Journal of Clinical Endocrinology and Metabolism,* Hamilton et al. from the University of Washington (Seattle) reported on the incidence of hyperparathyroidism in individuals internally exposed to ^{131}I from the Hanford Nuclear Site between 1944 and 1957. The researchers used as their database those individuals participating in the Hanford Thyroid Disease Study, including a random selection of 5,199 persons born between 1940 and 1946 to mothers with usual residence in a specific area of eastern Washington state. Of this study group, 3,440 underwent an evaluation for hyperparathyroidism. The individual thyroid radiation doses, which could be estimated for 3,191 participants, ranged from 0.0029 to 2,823 mGy (mean, 174 mGy). The authors confirmed 12 cases of primary hyperparathyroidism (0.35%) in the total study population and found no

correlation between this incidence of hyperparathyroidism and increasing radiation dose. Nor did they find evidence that the internal ^{131}I exposure received by the group at young ages increased the lifetime risk of primary hyperparathyroidism. However, they noted that "the effect of different doses and conditions of exposure to ^{131}I on the risk of hyperparathyroidism remains to be defined."

Journal of Clinical Endocrinology and Metabolism

Nasolacrimal Duct Obstruction in ^{131}I-Treated Patients

Morgenstern et al. from Ohio State University (Columbus) reported in the September issue of *Ophthalmic Plastic and Reconstructive Surgery* (2005;21:337–344) on the role of the sodium iodide symporter (NIS) in the incidence of nasolacrimal duct obstruction seen in patients undergoing high-dose radioactive iodine treatment. The authors performed reverse transcriptase–polymerase chain reaction and immunohistochemical analyses to evaluate NIS expression in archived and fresh human tissue specimens. They found NIS protein expressed in the stratified columnar epithelial cells of the lacrimal sac and nasolacrimal duct, but not in the lacrimal gland, Wolfring and Krause glands, conjunctiva, canaliculus, or nasal mucosa. NIS-expressing columnar epithelial cells were absent but fibrosis was evident in lacrimal sacs from radioiodine-treated patients undergoing dacryocystorhinostomy. The authors concluded that NIS is present in the lacrimal sac and nasolacrimal duct, correlating to the anatomic areas of clinical obstruction that develop in patients undergoing high-dose ^{131}I therapy. They noted that this "suggests that NIS may be the vector of radiation-induced injury to the lacrimal system" and that this novel report of an ion transporter in the nasolacrimal outflow system raises new questions about the role the lacrimal sac plays in the modification of tears and in lacrimal outflow pathology."

Ophthalmic Plastic and Reconstructive Surgery

Stress MPI as a Predictor of Cardiac Events

In the October issue of *Circulation Journal* (2005;69:1223–1229), Fukuda and Moroi from the Toho University Medical Center (Tokyo, Japan) reported on a study of patients exhibiting transient left ventricle (LV) dilation on stress myocardial perfusion imaging. The study included 53 men in whom transient LV dilation was observed on exercise or pharmacologic challenge ^{201}Tl SPECT and who were followed for an average of 17 months. End points were cardiac death, congestive heart failure, acute coronary syndrome, or revascularization. Summed stress scores (SSS), summed rest scores, and summed difference scores were calculated from the images. The combined cardiac event rate was found to be 59% (76% for exercise stress; 47% for pharmacologic stress). A combination of a higher SSS and slow washout rate was the best predictor of cardiac events. The authors pointed to this predictive ability and to the association between a high cardiac event rate and transient LV dilation as evidence of the added value of ^{201}Tl stress myocardial perfusion imaging.

Circulation Journal

"Protective" High Blood Pressure in Exercise

Yamagishi et al. from the Osaka City University Graduate School of Medicine (Japan) reported in the October issue of the *American Heart Journal* (2005;150:790–795) on a study designed to assess whether high diastolic blood pressure during exercise may have a protective effect against exercise-induced myocardial ischemia. The study included 469 patients with sinus rhythm and known or suspected coronary artery disease who underwent exercise ^{201}Tl myocardial SPECT and coronary arteriography. High diastolic blood pressure was defined as diastolic blood pressure at peak exercise ≥90 mm Hg. Patients with high diastolic blood pressure during exercise showed a higher pressure-rate product during exercise than did patients with normal diastolic blood pressure. The reversibility score on ^{201}Tl imaging myocardial scan was also significantly smaller in patients with high diastolic blood pressure during exercise than in patients with normal diastolic blood pressure. The authors concluded that "high diastolic blood pressure during exercise has a potential protective effect against exercise-induced ischemia, although the mechanism of such effects remains to be determined."

American Heart Journal

MPI and Panic Disorder in CAD

In an article in the October 15 issue of the *American Journal of Cardiology* (2005;96:1064–1068), Fleet et al. from the Montreal Heart Institute, the Sacre-Coeur Hospital, and the University of Montreal (Canada) reported on a study using SPECT myocardial perfusion imaging to assess the association between panic attacks and ischemia in patients with coronary artery disease (CAD). The study included 65 patients with CAD (35 with panic disorder and 30 without) who had shown positive results on nuclear exercise stress testing. Each patient underwent a panic challenge test (inhalation of a mixture of 35% carbon dioxide and 65% oxygen) and were injected with ^{99m}Tc-sestamibi at the time of inhalation. Each patient then underwent SPECT myocardial perfusion imaging, with simultaneous electrocardiography and monitoring of heart rate and blood pressure. Patients remained on their medications, and although those with panic disorder were on average significantly younger than those in the control group, other variables characterizing

the 2 groups (gender, medications, exercise test results, baseline heart rate, and blood pressure) did not differ. Individuals with panic disorder were much more likely than controls to undergo a panic attack at inhalation (74% and 6.7%, respectively). Those patients with panic disorder who experienced a panic attack were also much more likely than controls who did not experience a panic attack to develop a reversible myocardial perfusion defect (80.9% and 46.4%, respectively). The authors concluded that despite cardiac medications, "panic attacks preferentially induced significant perfusion defects in patients who had CAD and panic disorder." In short, they said, "panic attacks in patients who have CAD appear to be bad for the heart."

American Journal of Cardiology

Effects of Trimetazidine in Coronary Artery Ectasia

Okudan et al. from Suleyman Demirel University (Isparta, Turkey) reported in the October issue of the *Saudi Medical Journal* (2005; 26:1573–1578) on the use of rest/stress ^{99m}Tc-methoxyisobutyl isonitrile (^{99m}Tc-MIBI) to assess the effects of trimetazidine (TMZ) on ischemic left ventricular function in patients with coronary artery ecstasia. The study included 17 patients (9 men, 8 women) who underwent coronary angiography and were diagnosed with CAE. Each patient also underwent ^{99m}Tc SPECT imaging before and 4 weeks after TMZ administration. The authors found that the global ejection fraction increased from 59.9% ± 8.9% before to 62.6% ± 8.3% after therapy, whereas the end-systolic and end-diastolic volumes decreased over this period (101.7 ± 23.5 to 95.1 ± 22.9 mL and 41.1 ± 14.3 to 36.4 ± 13.6 mL, respectively). Significant after-therapy increases were seen in relative tracer uptake in all segments. The authors concluded that the results of this study showed that TMZ improves myocardial function on rest/stress ^{99m}Tc-MIBI–gated SPECT during stress-induced ischemia in patients with CAE and that this technique can be used to monitor the effect of TMZ in such patients.

Saudi Medical Journal

SPECT and Post-Stress Myocardial Stunning

In the November issue of *Circulation Journal* (2005;69:1338–1345), Tanaka et al. from Tokyo Medical University (Japan) reported on electocardiogram-gated ^{99m}Tc-sestamibi SPECT in the evaluation of post-exercise and post-vasodilator stress myocardial stunning. The study included 179 patients with known or suspected coronary artery disease (CAD) who underwent ^{99m}Tc-sestamibi SPECT imaging with either exercise or pharmacologic (adenosine triphosphate) challenge stress. Electrocardiogram-gated SPECT images were acquired at more than 30 minutes and at 4 hours after stress, and perfusion and wall motion were evaluated. Myocardial stunning was seen in 24 patients (22 after exercise and 2 after pharmacologic stress). The transient wall motion abnormality after exercise was greater in patients with severe ischemia than in those with mild-to-moderate ischemia. For those undergoing pharmacologic stress, the magnitude of the transient wall motion abnormality did not correlate with the severity of the perfusion abnormality. A significant correlation was found between summed difference score and transient wall motion abnormality after exercise but not after pharmacologic challenge. The authors concluded that in ^{99m}Tc-sestamibi SPECT, myocardial stunning is frequently observed after exercise and correlates with the severity of myocardial ischemia, but that this correlation does not occur with adenosine triphosphate, which is regarded as a specific marker for severe CAD.

Circulation Journal

PET Mismatch as a Predictor in Chronic LV Dysfunction

Desideri et al. from the Giacomo Hospital (Castelfranco Veneto, Italy) reported in the October 4 issue of the *Journal of the American College of Cardiology* (2005;46:1264–1269) on a study designed to assess the determinants of mortality in a large group of patients treated for chronic ischemic cardiomyopathy and assessed for viable tissue by PET imaging. The study included 261 patients with ischemic cardiomyopathy who underwent ^{18}F-FDG imaging for tissue viability. On follow-up, 94 patients were revascularized and 167 were not, with the cardiac death rate significantly lower in the revascularized patients. As expected, those patients revascularized with viable myocardium had longer average survival than those with nonviable myocardium. In those who did not undergo revascularization but were treated pharmacologically, age and extent of perfusion–metabolism mismatch on PET predicted cardiac death during a median follow-up period of 2.1 years. The risk of cardiac death was not significantly increased when the extent of mismatch was ≤20% but was significantly increased when the extent of mismatch was >20%. The authors concluded that "medically treated patients with ischemic cardiomyopathy and large areas of viable myocardium on PET are at high risk for cardiac death."

Journal of the American College of Cardiology

Dopaminergic Degeneration and Urinary Symptoms in PD

Winge et al. from the Bispebjerg University Hospital (Copenhagen, Denmark) reported in the November issue of the *European Journal of Neurology* (2005;12:842–850) on the use of ^{123}I-FP-CIT SPECT imaging to assess a possible relationship between dopaminergic degeneration and lower urinary tract symptoms in

patients with Parkinson's diease (PD). The study included 18 patients with PD who underwent ^{123}I-FP-CIT SPECT imaging and full urodynamic evaluation and responded to a questionnaire on bladder symptoms, both under medication and after cessation of medication. Bladder symptoms were found to correlate with age as well as stage and severity of disease but not with tracer uptake in the striatum. Patients with bladder symptoms showed significantly lower uptake in the striatum than patients without lower urinary tract symptoms. The putamen/caudate ratio on SPECT correlated with lower urinary tract symptoms in patients with severe bladder dysfunction. Tracer binding did not correlate with urodynamic parameters. The authors concluded that these results "suggest that the presence of lower urinary tract symptoms is associated with the degeneration of the total number of nigrostriatal dopaminergic neurones, while the severity of bladder dysfunction is correlated with the relative degeneration of the caudate nucleus." The effects of medication on bladder control as evaluated by urodynamics, they noted, are believed to involve structures outside the basal ganglia.

European Journal of Neurology

BBB Permeability in Acute Hemorrhagic Stroke

In the October 17 issue of *Cerebrovascular Disease* (2005;20:433–437), Lamp et al. from the Edith Wolfson Medical Center (Holon, Israel) and Tel Aviv University (Israel) reported on the relative effectiveness of CT and DTPA SPECT in clarifying the correlation between blood–brain barrier (BBB) breakdown and outcomes in patients with intracerebral hemorrhage. The study included 27 patients with primary intracerebral hemorrhage who underwent CT and ^{99m}Tc-DTPA SPECT and were assessed by both the National Institutes of Health (NIH) and modified Rankin scoring on follow up. The resulting SPECT findings had a significant correlation with the modified Rankin score after 3 and 6 months, whereas the CT scan was directly correlated with the NIH score on days 1, 7, and 30. No correlation was found between the SPECT and CT imaging data. The authors concluded that the degree of BBB disruption as imaged by SPECT was directly correlated with late functional outcomes, whereas the CT scan had an inverse correlation with the late-outcome NIH score. They noted that these findings may have broad clinical implications.

Cerebrovascular Disease

PET and Inhaled Radioligands

van Waarde et al. from the Groningen University Medical Center (The Netherlands) reported in the October issue of *Chest* (2005;128:3020–3027) on a PET study using an inhaled β-adrenoceptor antagonist (S-^{11}C-CGP 12388) in an effort to better discriminate between alveolar and airway β-adrenoceptors. The study included 8 healthy volunteers who inhaled the tracer from a nebulizer, at baseline and after pretreatment with a β-adrenergic drug (salbutamol or pindolol). Each patient underwent 2 sets of PET scans, each consisting of a dynamic scan of the lungs and a whole-body scan to assess inhaled dose. Pulmonary uptake was quantified using a region-of-interest-based analysis. The authors found that drug pretreatment did not affect pulmonary deposition of the radioligand. Salbutamol accelerated the monoexponential washout of ^{11}C in the peripheral lung (mainly alveoli), the central lung (mainly airways), and the main bronchi. Pindolol induced an even larger increase in washout rates. They concluded that "The similar effects of pindolol and salbutamol on tracer kinetics suggest that accelerated washout is due to the blockade of β-adrenoceptors." This indicates that the interaction of drugs with airway β-adrenoceptors can be routinely visualized using PET scanning and an inhaled radioligand.

Chest

^{11}C-MET PET as a Monitor in Glioma Treatment

In the September issue of the *Journal of Neurosurgery* (2005;103:498–507), Nariai et al. from the Tokyo Medical and Dental University and the Metropolitan Institute of Gerontology (Tokyo, Japan) reported on a retrospective study designed to clarify the relationship between L-[methyl-^{11}C] methionine (^{11}C-MET) uptake on PET and tumor biological features. The study included 194 patients with cerebral glioma or suspected glioma who underwent PET scanning 20 minutes after injection of ^{11}C-MET. Uptake into the tumor was expressed as a ratio to contralateral healthy brain tissue (T/N ratio), and analyses were performed to determine MET uptake correlations with tumor pathologic features and prognoses. Significant differences were found in T/N ratios among nonneoplastic lesions, low-grade gliomas, and malignant gliomas. Significant correlations were found between patient survival and pretreatment T/N ratios. Among patients with malignant gliomas, MET uptake in postoperative tumor remnant was a significant predictor of survival differences. Malignant pathologic features correlated directly with areas of highest MET uptake, and the effectiveness of radiotherapy or chemotherapy was correlated with a significantly decreased T/N ratio in some tumor types. The authors concluded, "The ability of MET PET to reflect the biological nature of gliomas makes it an excellent method for monitoring active tumor tissue, and treatments based on its findings should provide a powerful clinical protocol in the course of glioma therapy."

Journal of Neurosurgery

PET/CT and Second Primaries at Initial Staging

Choi et al. from the Samsung Medical Center (Seoul, Korea) reported in the October 20 issue of the *Journal of Clinical Oncology* (2005; 23:7654–7659) on a study that compared the utility of whole-body ^{18}F-FDG PET/CT and conventional staging work-up in detecting second primary cancers at the time of initial staging in patients with a variety of tumors. The study included 547 patients who underwent ^{18}F-FDG PET/CT imaging for initial staging after a diagnosis of cancer. For those patients in whom abnormal findings were indicative of a secondary primary tumor on either PET/CT or conventional staging, additional diagnostic evaluation was performed. A total of 27 second primary malignant tumors were identified in 26 of the patients (4.8%). PET/CT found 45 lesions indicative of a second primary cancer. Of these lesions, 24 were second primaries, 7 were unexpected metastases, and 14 were benign. The sensitivity and positive predictive value of PET/CT in detecting a second primary cancer or an unexpected metastasis were 91% and 69%, respectively. Conventional staging, however, failed to identify 16 of the second primary cancers and 1 metastatic lesion. The authors concluded that with its high sensitivity, an additional diagnostic work-up is essential when PET/CT yields abnormal findings indicative of a second primary cancer at initial staging.

Journal of Clinical Oncology

Therapy

Paclitaxel After ^{111}In-mAbs in RIT

A special October 1 issue of the journal *Clinical Cancer Research* was devoted to innovations and current applications in radioimmunotherapy. Among these articles, Miers et al. from the University of California–Davis (*Clin Cancer Res.* 2005;11:7158s–7163s) focused on the potential for enhanced therapeutic effects of paclitaxel-synergized radiolabeled monoclonal antibodies (mAbs) in breast and prostate cancers. The study included an evaluation of the effects of paclitaxel on mAb uptake in patients and in mice. The first part of the study included 12 patients with breast or prostate cancer who were given 2 imaging doses of ^{111}In-DOTA-Gly3Phe-m170, separated by 1 week. Of these patients, 5 were also administered a single dose of paclitaxel 2 days after the second ^{111}In-DOTA-Gly3Phe-m170. The authors found that tumor-cumulated activity increased significantly for the second dose in each of these patients compared with those who were not paclitaxel treated. In a second part of the study, athymic mice with human breast cancer xenografts were administered either ^{111}In-DOTA-Gly3Phe-ChL6 alone or combined with 1 or more daily paclitaxel administrations. The mice given paclitaxel a day after radiolabeled mAB administration also showed an increase in tumor-cumulated activity. In neither humans nor mice was this enhanced tumor-cumulated activity accompanied by changes in cumulated activities in normal tissues.

Clinical Cancer Research

Fractionated Treatments in Prostate Cancer RIT

Vallabhajosula et al. from Weill Medical College of Cornell University (New York, NY) reported on dose fractionation to decrease myelotoxicity in ^{90}Y- and ^{177}Lu-labeled J591 monoclonal antibody radioimmunotherapy of prostate cancer in the October 1 issue of *Clinical Cancer Research* (2005;11:7195s–7200s). The study included 35 patients with prostate cancer who received 10–75 mCi/m^2 ^{177}Lu-J591, and 28 patients who received 5–20 mCi/m^2 ^{90}Y-J591. A total of 15 patients in the first group received 2–3 treatments of ^{177}Lu-J591, and 4 patients in the second group received 2–3 doses of ^{90}Y-J591. Patients were retreated after 2–4 months with the same dose as their original cycle. The authors found that multiple (2 or 3) administrations of ^{177}Lu-J591 (30–60 mCi/m^2) or ^{90}Y-J591 (17.5 mCi/m^2) over a 4- to 6-month period were tolerated with manageable thrombocytopenia. They noted that although a single large dose may deliver an optimal radiation dose and thereby kill a larger fraction of tumor cells, fractionated therapy offers the advantage of lower myelotoxicity and prolonged tumor response. They recommended that for ^{177}Lu-J591, dose fractionation in combination with taxanes should be considered as an alternative approach to achieve optimal therapeutic efficacy in patients with prostate cancer.

Clinical Cancer Research