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. Note that although we have divided the articles into therapeutic and diagnostic 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. 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.

Therapy

Mortality in Patients Treated for Hyperthyroidism

In an article published in the July 6 issue of the *Journal of the American Medical Association* (2005;294: 71–80), Franklyn et al. from the University of Birmingham (UK) reported on a study designed to determine whether radioiodine treatment is associated with increased mortality and to identify the effect of subsequent thyrotoxine (T4) treatment on these mortality rates. The study included 2,668 individuals (ages ≥ 40 years) who had been treated for overt hyperthyroidism with radioiodine and who were followed for almost 8 years. Deaths and causes of death were compared with expected age- and period-specific mortality. The authors found that 554 individuals died during the study period, compared with 487 expected deaths. They identified increased risks for all causes averaged and especially for circulatory deaths among those who did not require or had not yet progressed to T4 therapy. Mild hypothyroidism before therapy was also associated with an increased risk of mortality from ischemic heart disease. These increased risks were no longer present among those who underwent T4 therapy. The authors concluded that although patients treated with radioiodine for hyperthyroidism had increased mortality when compared with the general population, this increased risk was not evident during and after T4 therapy. These results indicated that "this supports treating hyperthyroidism with doses of radioiodine sufficient to induce overt hypothyroidism" and that "T4 replacement should be considered should this biochemical abnormality develop after radioiodine therapy."

Journal of the American Medical Association

Dose-Fractionated Epratuzumab in NHL

Linden et al. from the Lund University Hospital (Sweden) reported in the July 15 issue of *Clinical Cancer Research* (2005;11:5215–5222) on a study conducted to establish the feasibility, safety, optimal dosing, and preliminary efficacy of fractionated doses of epratuzumab, a DOTA-conjugated ^{90}Y-radiolabeled humanized anti-CD22 monoclonal antibody (mAb), as radioimmunotherapy (RIT) in non-Hodgkin's lymphoma. A total of 16 patients with B-cell lymphoma received ^{90}Y-epratuzumab with unconjugated epratuzumab once weekly for 2–4 weeks. ^{111}In-epratuzumab was also administered at first infusion for scintigraphic imaging and dosimetry. The objective response rate was 62%. Complete responses occurred in 25% of patients and were durable (defined as event-free survival during a follow-up period of from 14 to 41 months). Two patients who received 4 infusions experienced hematologic dose-limiting toxicity, and serum levels of the mAb increased with each dose. The authors concluded that 3 weekly infusions of this RIT regimen can be administered safely with only minor toxicity. Additional evidence that therapeutic response was seen mainly in patients with unequivocal CD22 tumor expression was cited as an important factor for future studies.

Clinical Cancer Research

Phase I Trial of ^{131}I-Labeled mAb in Colorectal Carcinoma

In the July 1 issue of *Clinical Cancer Research* (2005;11:4810–4817, 4818–4826), 2 articles from researchers at the Ludwig Institute for Cancer Research (Melbourne, Australia) detailed aspects of a phase 1 trial of ^{131}I-humanized monoclonal antibody (mAb) A33 (huA33) in patients with advanced colorectal cancer. The first study, by Scott et al., identified the excellent targeting characteristics of huA33 and cited the potential for targeted therapy of metastatic colorectal cancer. The second study, by Chong et al. was a phase 1 dose escalation trial of ^{131}I-huA33 radioimmunotherapy (RIT). The study included 15 patients who had been treated for metastatic colorectal carcinoma. Each patient received an initial dose of the ^{131}I-huA33 for biodistribution assessment and a second dose as therapy. To define the maximum tolerated dose (MTD), 3 patients were treated at 20 mCi/m^2, 3 at 30 mCi/m^2, 3 at 40 mCi/m^2, and 6 at 50 mCi/m^2. The MTD was determined to be 40 mCi/m^2, with 2 patients experiencing grade 3 thrombocytopenia and 1 experiencing grade 4 neutropenia at 50 mCi/m^2. No acute adverse events were noted. Excellent tumor-targeting of ^{131}I-huA33 was

seen in all patients and, at restaging, 4 patients had stable disease and 11 patients had progressive disease. The authors concluded that RIT using ^{131}I-huA33 shows promise in targeting colorectal tumors and that additional studies with this agent in combination with chemotherapy should be undertaken.

Clinical Cancer Research

Recovery of NIS Expression in Thyroid Cancer Cells

In an article e-published ahead of print in the July issue of *BMC Cancer*, Presta et al. from the University of Catanzaro Magna Graecia (Italy) reported on an in vitro study of the use of gene expression therapy to aid in the recovery of sodium/iodide symporter (NIS) function and facilitate radioiodine uptake and concentration in the treatment of poorly differentiated thyroid cancer. The authors stably transfected anaplastic thyroid carcinoma ARO cells with a Pax8 gene expression vector. After a quantitative reverse transcriptase–polymerase chain reaction was performed to assess thyroid-specific gene expression, the presence of NIS protein was detected by Western blot and localized by immunofluorescence in selected clones. An iodide uptake assay was also performed. The authors found that the cloned cells overexpressing Pax8 showed the reactivation of several thyroid-specific genes, including NIS, pendrin, thyroglobulin, thyroperoxidase, and thyroid transcription factor 1, with NIS protein localized in cell cytoplasm and membrane. These cells also showed a slower rate of cell growth. The authors concluded that "these finding demonstrate that induction of Pax8 expression may determine a partial redifferentiation of thyroid cancer cells, including the recovery of iodide uptake, a fundamental requisite for a radioiodine-based therapeutic approach for thyroid tumors."

BMC Cancer

Retinoic Acid and Advanced Thyroid Cancer

In a review article published in the July issue of *Current Pharmaceutical Design* (2005;11:25–31), Coelho et al. from the Federal University of Rio de Janeiro (Brazil) reported on studies documenting the effects of retinoic acid in advanced thyroid cancer. Retinoic acids are natural derivatives of vitamin A and play roles in modulating growth and differentiation in many cell types. Despite combinations of surgery and radioiodine ablation and subsequent thyroid-stimulating hormone suppressive therapy, 20%–40% of patients with well-differentiated thyroid carcinomas experience recurrence. The authors point to in vitro studies that indicate that retinoic acids can induce redifferentiation of thyroid carcinoma cell lines and exert antiproliferative actions, including inhibition of mitosis and induction of apoptosis. Clinical studies indicate that iodide uptake may be restimulated after retinoic acid administration in 20%–50% of patients with radioiodine nonresponsive thyroid carcinoma, and studies with longer follow-up periods suggest that tumor stabilization or regression may result from this well-tolerated therapeutic regimen.

Current Pharmaceutical Design

Glucocorticoids and Thyroid Function in ^{131}I Treatment for Graves Disease

Jensen et al. from Odense University Hospital (Denmark) reported in the July issue of the *European Journal of Endocrinology* (2005;153: 15–21) on a retrospective study to determine whether glucocosteroids administered to patients with Graves disease during ^{131}I therapy affect thyroid function. Glucocosteroids are often administered to such patients as prophylaxis for or to treat mild ophthalmopathy during therapy. The study included 207 previously untreated patients with Graves disease undergoing ^{131}I therapy: 96 patients who received prednisolone for mild or previous mild ophthalmopathy or the presence of risk factors for developing this complication and 111 patients who did not receive prednisolone prophylaxis. At 1-year follow-up, patients were classified as hypothyroid, euthyroid, or hyperthyroid. For those who received prednisolone, these numbers were 23, 35, and 38, respectively, whereas the corresponding numbers for those who did not receive prednisolone were 26, 40, and 45, respectively. Cure rates were almost identical between the 2 groups, as were the median time intervals until development of hypothyroidism or recurrence of hyperthyroidism. The authors concluded that, "although glucocorticoids in some contexts seem to attenuate the radiation-induced oxidative stress this had no impact on the final outcome following ^{131}I therapy of patients with Graves disease."

European Journal of Endocrinology

^{177}Lu- and $^{67/64}$Cu-Labeled RIT Techniques

In the July 15 issue of *Clinical Cancer Research* (2005;11:5112–5120), Grunberg et al. from the Paul Scherrer Institute (Villigen, Switzerland) and University Hospital Basel (Switzerland) reported on a bioevaluation of ^{177}Lu- and $^{67/64}$Cu-labeled recombinant fragments of antibody chCE7 for radioimmunotherapy, including assessment of PET imaging of L1-CAM-positive tumors in a mouse model. The technique shows promise for tumors in which the L1 cell adhesion protein is overexpressed, such as neuroblastomas, renal cell carcinomas, ovarian carcinomas, and endometrial carcinomas. The authors found that ^{177}Lu- and $^{67/64}$Cu-labeled recombinant immunoconjugates showed different in vivo behaviors, with a $^{67/64}$Cu-labeled immunoconjugate appearing to be the most favorable of those studied, because of superior tumor/kidney ratios.

Clinical Cancer Research

Diagnosis

SPECT Bone Marrow Imaging in RT Planning for Gynecologic Cancers

In an article e-published ahead of print on July 15 in *Radiotherapy and Oncology*, Roeske et al. from the University of Chicago (IL) reported on a case study incorporating SPECT bone marrow imaging into the treatment planning process to reduce the volume of bone marrow irradiated in patients receiving intensity-modulated whole-pelvic radiation therapy. The authors first performed planning CT imaging in a patient with early-stage endometrial cancer, followed by a ^{99m}Tc-sulfur colloid SPECT scan of the pelvis. Using image fusion software, the SPECT scan was coregistered with the planning CT scan and used to delineate regions of active bone marrow. An intensity-modulated radiation therapy plan was generated to provide coverage of tumor volume and spare areas of active bone marrow and other normal pelvic structures. For doses >30 Gy, this technique reduced the dose to areas of high active bone marrow density in the lumbar vertebrae, sacrum, and medial iliac crests by 50% compared with conventional planning. Tumor radiation dose was not compromised. The authors concluded that these results suggest that SPECT bone marrow imaging is a useful adjunct to intensity-modulated whole-body radiation therapy planning in gynecologic patients.

Radiotherapy and Oncology

3D-SSP SPECT Analysis of CBF in Dementias

Mito et al. from the Asahikawa Red Cross Hospital (Hokkaido, Japan) reported in the August issue of *Clinical Neurology and Neurosurgery (*2005;107:396–403) on a study using 3-dimensional stereotactic surface projection (3D-SSP) SPECT analysis to compare cerebral blood flow in patients with dementia with Lewy bodies (DLB; 6 patients), Parkinson's disease with dementia (PDD; 7 patients), Parkinson's disease without dementia (PD; 21 patients), and Alzheimer's disease (AD; 12 patients) and in 12 healthy individuals. All participants underwent ^{123}I-iodoamphetamine SPECT imaging, and the results were analyzed with 3D-SSP software. The authors found that regional patterns of blood flow reduction in the brain were different among patients with DLB, PD, and AD. Greater blood flow reduction was observed in patients with DLB, although those with DLB and PDD showed similar reduction patterns. The authors concluded that these patterns "suggest different and disease-specific combinations of underlying pathological and neurochemical processes" and that imaging techniques show great promise in assisting in the clinical differentiation of these types of dementia.

Clinical Neurology and Neurosurgery

SPECT and ECG as Metrics for LVEF

Habash-Bseiso et al. from the Marshfield Clinic (WI) reported in the May issue of *Clinical Medicine and Research* (2005;3:75–82) on a study comparing the efficacy of 2-dimensional echocardiography and electrocardiogram-gated SPECT with that of left ventricular contrast angiography for the evaluation of left ventricular ejection fraction (LVEF). The retrospective study included 534 patients from a large, community-based clinic who underwent angiography as well as echocardiography or SPECT (all imaging within a 1 month period) for evaluation of LVEF. Noninvasive LVEF values were compared with those obtained by angiography. The authors found that the angiographic LVEFs were significantly correlated with both echocardiographic and SPECT LVEFs, but that both echocardiographic and SPECT LVEFs were somewhat lower. They noted widely fluctuating differences in some of these readings, but concluded that although lower, the noninvasive techniques appeared to accurately assess depressed LVEFs (<40% and <35%). Additional research and institution-specific assessments were recommended.

Clinical Medicine and Research

^{99m}Tc-ECD SPECT Assessment in Hydrocephalus

Navak et al. from the All India Institute of Medical Sciences (New Delhi) reported in the May–June issue of *Pediatric Neurosurgery* (2005; 41:117–121) on the use of ^{99m}Tc-ECD SPECT to study regional cerebral perfusion before and after ventriculoperitoneal shunt placement in children with hydrocephalus. The study included 17 children (11 boys, 6 girls; median age, 24 months) with hydrocephalus who were scheduled for ventriculoperitoneal shunt placement. In 10 children the hydrocephalus was congenital, was secondary to tumor in 5, and a result of infection in 2. ^{99m}Tc-ECD SPECT imaging was performed before and after placement, and changes in cerebral perfusion and ventricular size were compared. After surgery, 14 children (82%) showed improvement in cerebral perfusion after shunting, and 12 of these showed a decrease in ventricular size. The authors found that cerebral perfusion improved in the majority of the children after cerebrospinal fluid diversionary procedures, and that factors such as duration of hydrocephalus and decreased ventricular size did not influence this improvement. They concluded that "SPECT can therefore prove to be a valuable tool for objective assessment of improvement in cerebral perfusion in children with hydrocephalus secondary to various etiologies following surgical or medical interventions."

Pediatric Neurosurgery

Promising Bivalent Anti-HER-2 Affibody

Steffen et al. from Uppsala University (Sweden) reported in the June issue of *Cancer Biotherapy and Ra-*

diopharmaceuticals (2005;20:239–248) on in vitro characterization of a bivalent anti-human epidermal growth factor receptor (HER-2) with potential for radionuclide-based diagnostic applications in breast and ovarian cancers. The authors compared mono- and bivalent ligands when radiolabeled with ^{125}I. The bivalent molecule was retained longer in the cell and, at approximately one tenth the size of the monoclonal antibody trastuzumab, is a "promising candidate for radionuclide-based detection of HER-2 expression in tumors." The authors noted that ^{125}I was used in this study as a surrogate marker for the diagnostically relevant radioisotopes ^{123}I for SPECT/gamma camera imaging and ^{124}I for PET.

Cancer Biotherapy and Radiopharmaceuticals

^{18}F-FDG Biodistribution in Tumor and Infection

In an article published in the June issue of *Cancer Biotherapy and Radiopharmaceuticals* (2005,20:310–315), Kok et al. from Radboud University Nijmegen Medical Center (The Netherlands) used PET to compare the dynamic distribution of ^{18}F-FDG in malignant and *Escherichia coli* lesions in a rat model. Dynamic ^{18}F-FDG PET imaging was performed up to 4 hours after injection of ^{18}F-FDG, standardized uptake values (SUVs) were calculated, and biodistribution was calculated in rats with both tumor and infection. The authors found that dynamic PET visualized both tumor and infection. ^{18}F-FDG uptake in infection was faster and greater than in tumor lesions. ^{18}F-FDG uptake in tumor reached an SUV of 0.8 ± 0.3 at 60 minutes and reached 1.6 ± 0.2 at 45 minutes in infectious lesions, both remaining constant until 4 hours after injection. Although differences in uptake and initial kinetics were similar, the washout rate of ^{18}F-FDG from the lesions was similar over time. The authors cautioned that "retention of FDG in the inflammatory lesion indicated that dual time-point imaging does not necessarily resolve diagnostic pitfalls for FDG-PET in oncology in order to discriminate between malignant tumorous and benign infectious lesions."

Cancer Biotherapy and Radiopharmaceuticals

PET SUVs as Predictors in NSCLC

Cerfolio et al. from the University of Alabama at Birmingham reported in the July issue of the *Journal of Thoracic and Cardiovascular Surgery* (2005;130:151–159) on a study assessing whether the standard uptake value (SUV) of a pulmonary nodule is an independent predictor of biologic aggressiveness in patients with non–small cell lung cancer (NSCLC). The study included 315 patients who underwent both PET and CT imaging. Those with suspicious nodal or systemic findings underwent biopsy, and when indicated, resection with complete lymphadenectomy. The results indicated that patients with high maximum SUVs (≥10) were more likely to have poorly differentiated tumors at a more advanced stage and were less likely to have their disease completely resected. Maximum SUV was the best predictor of disease-free survival and overall survival. Patients with stage IB and stage II disease with a maximum SUV greater than the median for their respective stages had lower disease-free survival at 4 years. When results were used to divide patients into low- and high-maximum SUV groups, the actual 4-year survival for patients with stage IB NSCLC was 80% and 66%, respectively; for stage II disease was 64% and 32%, respectively; and for stage IIIA disease was 64% and 16%, respectively. The authors concluded that the maximum SUV of an NSCLC nodule on dedicated PET "is an independent predictor of stage and tumor characteristics" and is a "more powerful independent predictor than the TNM stage for recurrence and survival for patients with early-stage resected cancer."

Journal of Thoracic and Cardiovascular Surgery

Function of Sigma Receptors in Parkinson's Disease

Mishina et al. from the Nippon Medical School Chiba-Hokusoh Hospital (Japan) reported in the August issue of *Acta Neurologica Scandinavica* (2005;112:103–107) on a study using ^{11}C-SA4503 PET to investigate the mapping of sigma receptors in Parkinson's disease (PD) and to determine whether these receptors are involved in the damaged dopaminergic system seen in PD. The study included 6 patients with PD and 7 healthy volunteers. A dynamic series of PET imaging was performed with arterial blood sampling, followed by computation of the binding potential of ^{11}C-SA4503. Results indicated that binding potential in patients with PD was significantly lower on the more affected than the less affected side of the anterior putamen. However, no significant difference was noted in overall binding potential in patients and controls. The authors concluded that release of dopamine is reduced asymmetrically in the putamen of patients with early PD and that ^{11}C-SA4503 PET is a promising indicator of presynaptic dopaminergic damage in PD.

Acta Neurologica Scandinavica

New Ligands for Norepinephrine Transporter Imaging

In the July issue of the *Journal of Neurochemistry* (2005;94:337–351), Ding et al. from the Brookhaven National Laboratory (Upton, NY) reported on the synthesis and evaluation of several new ligands for PET imaging of the norepinephrine transporter (NET) system and on initial imaging in baboons. After investigating a series of ligands, the authors focused on analogs of methylreboxetine (MRB) and identified the superiority of (S,S)-^{11}C-MRB and others as potential NET ligands for PET imaging.

Journal of Neurochemistry