CMS Posts PET Coverage for Alzheimer's

The Centers for Medicare & Medicaid Services (CMS) announced on September 15 that it has posted (the equivalent of formally enacting) expanded Medicare coverage of PET to include some Medicare beneficiaries with suspected Alzheimer's disease (AD) and to include other beneficiaries at risk for AD who are enrolled in large and easily accessible clinical trials. Medicare beneficiaries who meet specific criteria may participate in a clinical trial and receive a PET scan while CMS continues to review evidence about the benefits of PET in additional populations. The National Coverage Decision expands the coverage of PET to include beneficiaries who meet the diagnostic criteria for both AD and frontotemporal dementia, who have been evaluated for specific alternate causes of dementia, and for whom the cause of the clinical symptoms remains uncertain. Medicare coverage of PET also includes other patients with suspected AD who enroll in a large, CMS-approved clinical trial.

"Together with outside experts and other agencies we examined the available data and determined that we ought to approve coverage for patients who've been worked up but whose diagnosis is uncertain," said CMS Administrator Mark B. McClellan, MD, PhD. "We also concluded that the technology is promising for patients with early dementia, but is only reasonable and necessary in the context of a peer-reviewed clinical trial that will ensure that the technology is properly used to help families and doctors to diagnose and manage their cases, and will develop evidence of the value of the technology for particular populations and the safeguards necessary to ensure patient protection. We're moving forward on both fronts."

The posting came after an extensive review that included a number of expert panels, literature reviews, public hearings, and substantial input from the nuclear medicine community. CMS press releases noted that this coverage decision was the first under the Medicare Modernization Act of 2003 requirements to post a draft of the decision memorandum, have a 30-day public comment period, and then post the final decision memorandum and implement the policy within 90 days of posting the draft decision. The final decision memorandum is available on the CMS Web site at: www.cms.hhs.gov/coverage.

Centers for Medicare & Medicaid Services

IAEA Report on ^{99m}Tc CNS Agents

On September 15 the International Atomic Energy Agency (IAEA) released *Development of ^{99m}Tc Agents for Imaging Central Neural System Receptors*, as part of the agency's technical report series. "Radiopharmaceuticals for imaging the receptors in the brain are of great interest in the management of several receptor-related diseases, such as epilepsy, Alzheimer's disease, Parkinson's disease, and depression and other psychiatric disorders," said an IAEA statement. "Technetium-99m is the ideal radioisotope for imaging, due to its low cost, its easy and universal availability through commercially available generator systems, and its physical decay characteristics."

The publication is the result of the work of a coordinated research program aimed at the development of ^{99m}Tc-labeled central neural system receptor imaging agents. The report summarizes work carried out by different groups within the research program. Research projects presented by participants include the development and evaluation of serotonin-, benzodiazepine-, and dopamine receptor ligands, the study of novel cores for ^{99m}Tc labeling, and molecular modeling. The 198-page report may be downloaded in PDF format from the IAEA Web site at www.pub.iaea.org/MTCD/publications/PDF/TRS426_web.pdfFull Text.

International Atomic Energy Agency

NRC Seeks to Tighten Export–Import Rules on High-Risk Materials

The Nuclear Regulatory Commission (NRC) is proposing tougher licensing requirements for the export or import of high-risk radioactive materials that could be used in so-called "dirty bombs" or other terrorist weapons. Commission Chair Nils J. Diaz issued a statement on September 15, and the text of the proposed rule appeared in the next day's *Federal Register* (2004;69:55785–55790). The proposed rule would implement export–import provisions of the Code of Conduct on the Safety and Security of Radioactive Sources adopted last year by the International Atomic Energy Agency. The new NRC regulations would require specific licenses for all exports and imports of high-risk radioactive materials as defined in the Code of Conduct.

The proposed rule would include bulk materials as well as materials in sealed sources. Anyone in the United States wishing to export or import these materials would be required to apply for NRC approval. Under current NRC regulations, these radioactive materials may be exported or imported under a general license, which does not require filing an application to the NRC or the issuance of licensing documents. Among the 15 isotopes identified as high risk were ^{241}Am, ^{60}Co, ^{137}Cs,

^{130}Gd, ^{75}Se, and ^{90}Sr. Specific quantities are listed in the proposed rule.

Comments on the changes were accepted until October 16. Additional information on the status of the rule is available at the NRC Web site at www.nrc.gov.

U.S. Nuclear Regulatory Commission

First NIH Pioneer Awards Focus on Molecular Sciences

Elias Zerhouni, MD, director of the National Institutes of Health (NIH) announced in a telebriefing on September 28 the 9 recipients of the first-ever NIH Director's Pioneer Award program. The awards were created to support individual scientists and thinkers who have highly innovative ideas and approaches to contemporary challenges in medical research. The recipients will each be awarded $500,000 in direct costs per year for 5 years. During that period, they will spend the majority of their time conducting high-risk, high-impact research with the potential to make significant contributions to knowledge in human health.

Awardees included Larry Abbott, PhD (Brandeis University, Waltham, MA); George Daley, MD, PhD, (Children's Hospital Boston, Boston, MA); Homme Hellinga, PhD (Duke University Medical Center, Durham, NC); Joseph McCune, MD, PhD, (J. David Gladstone Institutes, San Francisco, CA), Steven McKnight, PhD, (University of Texas Southwestern Medical Center, Dallas, TX); Chad Mirkin, PhD, (Northwestern University, Evanston, IL); Rob Phillips, PhD, (California Institute of Technology, Pasadena, CA); Stephen Quake, PhD, (California Institute of Technology, Pasadena, CA); and Sunney Xie, PhD, (Harvard University, Cambridge, MA). The 9 recipients represent a broad spectrum of scientific disciplines, including quantitative and mathematical biology, pathogenesis, epidemiology and translational clinical research, molecular and cellular biology, integrative physiology, instrumentation, and bioengineering. Most are currently conducting research that focuses on health and illness at the molecular level.

Applicants underwent a rigorous nomination and selection process in which they were asked to demonstrate commitment to accepting considerable risk in addressing critically important scientific questions relevant to the mission of the NIH. External evaluators from a range of scientific disciplines screened approximately 1,000 nominations and recommended that a subset of 240 nominees be invited to submit award applications. Further review by external evaluators resulted in the selection of 21 candidates who were invited to the NIH for interviews and to present their ideas. Applicants were evaluated based on evidence of scientific innovation and creativity; testimony of intrinsic motivation, enthusiasm and intellectual energy; and potential for scientific leadership and evidence of, or potential for, effective communication skills.

More information on the NIH Director's Pioneer Award Program, including awardee information, is available at http://nihroadmap.nih.gov/highrisk/index.asp.

National Institutes of Health

NIBIB, Hughes to Fund Interdisciplinary Training

The Howard Hughes Medical Institute (HHMI) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health (NIH) announced on September 27 an interdisciplinary PhD program that will invest up to $35 million in start-up funds and sustaining support for graduate training programs that integrate the biomedical sciences with the physical sciences and engineering. HHMI will award up to ten 3-year grants of as much as $1 million each to support the development and early phases of the interdisciplinary programs. NIBIB will provide 5 additional years of support to the HHMI grantees through peer-reviewed institutional training grants. Building on work begun by the Whitaker Foundation, the National Science Foundation, and the Burroughs Wellcome Fund, HHMI and NIBIB have created a new model to support the initiation, development, and maintenance of new graduate programs to provide upcoming biomedical scientists with cross-disciplinary knowledge and skills.

The competition for grants opened in October, and grants will be awarded in November 2005. All U.S. institutions that grant PhD degrees in the biological sciences will be eligible. "We're looking for training programs that provide strategies to eliminate or lower barriers between seemingly disparate scientific disciplines," said Peter J. Bruns, HHMI vice president for grants and special programs. For more information about the grants programs, view the program announcement at www.hhmi.org/grants/institutions/nibib.html.

National Institute of Biomedical Imaging and Bioengineering

NIH Opens New Clinical Research Hospital

The National Institutes of Health (NIH) celebrated the opening of the Mark O. Hatfield Clinical Research Center on September 22. At the dedication ceremony, the new facility was called "the most significant addition to the NIH campus in more than 50 years." The 870,000-square-foot Hatfield Center connects to the existing Warren Grant Magnuson Clinical Center, which opened its doors to patients in 1953 and has seen more than 350,000 participants in clinical studies from every state and around the world.

"We have patients who come here who've lost hope for any other treatment," said NIH Director Elias A. Zerhouni, MD. "This is why we really are very pleased to have received the support of Congress, the support of the American public, and

most importantly, the thousands of patients who come from all around the country and the world to participate as partners in clinical research."

Named in honor of former Senator Mark O. Hatfield, who served in Congress for 30 years and provided support to NIH and clinical research, the new hospital will allow for cutting-edge research and patient care. The Hatfield Center will open with approximately 240 inpatient beds and 80 day-hospital stations. Laboratories and patient rooms are highly flexible and can quickly adapt to meet new requirements and changing priorities.

Laboratory and office moves are currently underway, and patients will move into the new hospital in December.

National Institutes of Health

National Cancer Institute Announces Major Commitment to Nanotechnology for Cancer Research

The National Cancer Institute (NCI) announced on September 13 a new $144.3 million, 5-year initiative to develop and apply nanotechnology to cancer. "Nanotechnology has the potential to radically increase our options for prevention, diagnosis, and treatment of cancer," said Andrew von Eschenbach, MD, director of the National Cancer Institute. "NCI's commitment to this cancer initiative comes at a critical time. Nanotechnology supports and expands the scientific advances in genomics and proteomics and builds on our understanding of the molecular underpinnings of cancer. These are the pillars which will support progress in cancer."

To carry out this initiative, NCI is forming the NCI Alliance for Nanotechnology in Cancer, a comprehensive, integrated initiative encompassing researchers, clinicians, and public and private organizations that have joined forces to develop and translate cancer-related nanotechnology research into clinical practice.

NCI Alliance consists of 4 major program activities:

(1) Centers of Cancer Nanotechnology Excellence: The centers will work to integrate nanotechnology development into basic and applied cancer research. Each center will be affiliated with a NCI Comprehensive Cancer Center, university, or research center of engineering and physical science. It is hoped that these centers will bridge gaps in the development pipeline from materials discovery to preclinical testing.

(2) Multidisciplinary research teams: Investigators with basic science and clinical backgrounds will require training to optimize the development and translation of nanotechnologies toward clinical oncology applications. The NCI will initially use existing career development mechanisms to direct talent to this area, create incentives for cross-disciplinary research, and foster collaboration through training.

(3) Nanotechnology platforms for cancer research: Over the next 5 years, investigator-initiated and -directed project research will be supported in 6 key programmatic areas: molecular imaging and early detection, in vivo imaging, reporters of efficacy (e.g., real-time assessment of treatment), multifunctional therapeutics, prevention and control, and research enablers (opening new pathways for research).

(4) Nanotechnology Characterization Laboratory: Research here will perform and standardize the pre-clinical characterization of nanomaterials developed by researchers from academia, government, and industry and serve as a national resource and knowledge base for cancer researchers.

National Cancer Institute

ORNL Sets Image Resolution Record

Researchers at Oak Ridge National Laboratory (ORNL) and the Nion Company of Kirkland, WA, announced in September that for the second time this year they had set a world record for image resolution using their Z-contrast microscope. Nellist et al. were able to obtain image resolution at 0.6 Å, allowing scientists to look at individual atoms of silicon in a crystal. The research results were reported in the September 17 issue of *Science* (2004;305:1741). The resolution topped the previous record of 0.7 Å set with the same 300-kv Z-contrast scanning transmission electron microscope. The article included images of pairs of silicon atom columns in a crystal.

Oak Ridge National Laboratory

From the Literature

Each month the editor of Newsline selects articles on therapeutic, diagnostic, research, and practice issues in nuclear medicine 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.

Diagnosis

HIV Dementia Mechanism Assessed

In a study e-published ahead of print on August 19 in *Brain*, Wang et al. from the Brookhaven National Laboratory (Upton, NY) reported on the elucidation of a key mechanism in the brains of individuals with HIV cognitive motor complex, more commonly called HIV dementia. The authors assessed dopamine D_2 receptors and transporters in 15 individuals with HIV (aged 44.5 $\pm$ 11 years) and in 13 seronegative controls (aged 42 $\pm$ 12 years). Participants were evaluated with ^{11}C-cocaine PET and ^{11}C-raclopride PET to assess availability of dopamine D_2 transporters and receptors, respectively. HIV patients with associated dementia had significantly lower transporter ability

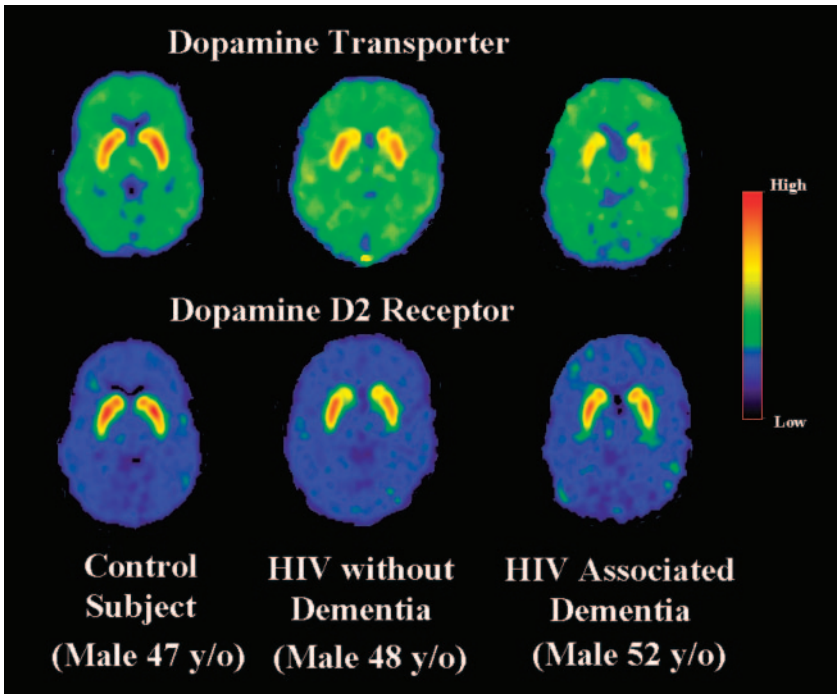

FIGURE 1. PET scans showing dopamine transporters (top row) and dopamine D_2 receptors (bottom row) in a 47-year-old control subject (left), a 48-year-old HIV subject without dementia (middle), and a 52-year-old HIV subject with dementia (right), at the level of the basal ganglia. Images are scaled with respect to the maximum value obtained in the control individual and presented using the rainbow scale (red = high value; violet = low value). The HIV individuals with dementia showed significantly lower dopamine transporter availability bilaterally in the putamen and in the ventral striatum, but only mild and nonsignificant decreases in the caudate compared with the seronegative controls. The nondemented HIV patients, however, showed no significant decreases in dopamine transporters in the basal ganglia. Dopamine D_2 receptor availability did not differ between the HIV and the control subjects in any of the regions. Courtesy of Brookhaven National Laboratory.

in putamen (–19.3) and ventral striatum (–13.6%) than seronegative controls. Higher plasma viral load in HIV dementia patients correlated with lower levels of dopamine transporters in the caudate and putamen. Only mild and nonsignificant differences were noted in dopamine D_2 receptor availability in all groups studied (Fig. 1).

"Our results offer the first evidence of dopamine terminal injury—specifically injury to dopamine transporters—in HIV dementia patients," said Wang. "This suggests that a decrease in transporters may contribute to the disease process. We believe our findings also indicate a new direction for treatment." The findings indicate that HIV patients, especially those with severe cognitive motor deficits, may benefit from dopamine-enhancing treatments. "Studies have shown, however, that some of these agents may actually exacerbate HIV-induced neurotoxicity, but antioxidants may block this mechanism. Further studies should focus on adjunctive approaches combining drugs in both classes," said Wang. "Viral suppression seems to correlate with less injury to the dopamine system. Because of this correlation, future studies should look at whether viral suppression after antiretroviral treatment can lead to recovery of deficits in the dopamine system."

Brain

Whole-Body vs. Thoracic PET in Lung Cancer

Aquino and Fischman from the Massachusetts General Hospital (Boston, MA) reported in the September issue of *Chest* (2004;126: 755–760) on a retrospective study comparing whole-body (skull to midthigh) ^{18}F-FDG PET with thoracic (skull base to kidneys) ^{18}F-FDG PET in patients evaluated for a solitary pulmonary nodule or newly diagnosed lung cancer in whom PET had detected distant extracranial and extrathoracic metastases. A study population of 1,026 was derived from previous studies, with 35 patients found to have distant extracranial metastases from lung cancer. These patients were staged according to the TNM classification based on either thoracic PET or whole-body PET findings. Of the 26 patients assessed as having true metastases on the basis of whole-body PET findings, 25 had metastatic lesions observed within the confines of thoracic PET. Only 1 patient had an isolated metastasis that was detected by whole-body PET only. The authors concluded that "thoracic PET, when compared to whole-body PET, is 96.2% sensitive for detecting extrathoracic metastases in patients with newly diagnosed non-small cell lung cancer." They noted that with the recent introduction of hybrid systems, the use of thoracic PET/CT might be considered to minimize radiation dose.

Chest

PET/CT vs PET in NSCLC Staging

In the September issue of *Annals of Thoracic Surgery* (2004;78:1017–1023), Cerfolio et al. from the Birmingham Veterans Administration Hospital (AL) reported on a comparison of the accuracy of PET/CT with that of PET alone in staging of patients with non-small cell lung cancer (NSCLC). The study included 129 patients who underwent ^{18}F-FDG PET/CT for NSCLC staging and subsequent assignment of TNM status. Within 2 weeks of this imaging, each patient underwent dedicated PET, with subsequent assignment of TNM status based on these findings. The

most recent CT scan was visually correlated with both studies. All patients underwent biopsies of suspicious N2 or N3 lymph nodes or distant metastases. If negative, pulmonary resection with lymphadenectomy was performed. On the basis of histologic results, the authors found that PET/CT was a better predictor than PET alone for all stages of cancer, although the difference was statistically significant only in stages 1 and 2. They concluded that "integrated PET/CT using ^{18}F-FDG better predicts stage 1 and 2 disease as well as the T and N status of patients with NSCLC when compared with dedicated PET alone. It is more accurate at some nodal stations but still only achieves an accuracy of 96% and 90% for the N2 and N1 nodes, respectively."

Annals of Thoracic Surgery

Low-Dose Assessment of Intrathecal Drug System Patency

In a study e-published on August 24 ahead of print in *Spinal Cord*, Crawley et al. from the Stoke Mandeville Hospital (Aylesbury, UK) reported on a retrospective study designed to evaluate a low-dose radioisotope imaging procedure for assessment of implanted intrathecal drug delivery and to compare the radiation dose and diagnostic value with those of other studies using higher radiation doses. The study included 11 patients with spinal injuries and subcutaneous drug delivery systems who were experiencing uncontrolled spasm. They were assessed for catheter failure using 40 MBq ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) SPECT, which constituted a low-dose compared with more frequently used assessment measures. The technique revealed catheter blockages in 6 patients and identified sites of blockage, as well as showing that the catheter was functioning normally in the remaining 5 patients. The radiation effective dose was estimated at 1.3 mSv. The authors concluded that "radioisotope investigation using a reduced administered dose of 40 MBq ^{99m}Tc-DTPA, formulated according to a strict radiopharmaceutical protocol, provides a safe test for assessment of intrathecal drug delivery systems."

Spinal Cord

Postradiation ^{99m}Tc-Glucoheptonate Brain SPECT

Both PET and SPECT continue to prove beneficial in enhancing outcomes by providing valuable information that allows the differentiation between recurrent tumor and postradiation necroses and scarring. In a study published in the September issue of *Australasian Radiology* (2004; 48:296–301), Barai et al. from the All India Institute of Medical Sciences (New Delhi) reported on a study using ^{99m}Tc-glucoheptonate brain SPECT to distinguish recurrent disease from postradiation gliosis. The study included 73 patients with primary malignant brain tumors who had undergone radiotherapy and subsequent SPECT imaging. SPECT indicated recurrent tumor in 55 patients and no recurrent disease in the remaining patients. The clinical course was consistent with recurrence in 51 of the 55 patients and was consistent with radiation necrosis in the remaining patients (including the 4 who had positive SPECT results). The authors concluded that "^{99m}Tc-glucoheptonate brain SPECT is a sensitive and reliable diagnostic modality to differentiate recurrent tumor from postradiation gliosis."

Australasian Radiology

Antibody Imaging of Appendicitis

Passalaqua et al. from the Children's Hospital Medical Center of Akron (OH) reported in the September issue of the *Journal of Pediatric Surgery* on an investigation of the potential role of a ^{99m}Tc-labeled antigranulocyte murine antibody Fab' fragment (sulesomab) as an imaging agent in children with suspected acute nonclassic appendicitis. The study included 40 children with suspected acute nonclassic appendicitis who underwent serial planar and SPECT imaging at 15–30 minutes and 1, 2, and 4 hours after sulesomab injection. Imaging results indicated appendicitis in 21 patients in whom the diagnosis was confirmed at surgery. Signs and symptoms resolved in the remaining patients, and they were considered to not have appendicitis. Sulesomab imaging was found to have a 95% sensitivity, 90% specificity, 95% negative predictive value, and 90% positive predictive value for acute appendicitis. In 78% of patients, sulesomab accurately detected or excluded acute appendicitis and would have changed management plans. No side effects or antibody responses were noted. The authors concluded that, "In pediatric patients with suspected nonclassic appendicitis, management decisions incorporating sulesomab imaging provided benefit in separating surgical from nonsurgical patients."

Journal of Pediatric Surgery

Nuclear Medicine Imaging in Dolphins

In a study reported in the October issue of the *Journal of Experimental Biology* (2004;207:3657–3665), Houser et al. from BIOMIMETICA (La Mesa, CA) reported on the use of functional and structural imaging to investigate the origins of special hearing and spatial navigation capabilities in bottlenose dolphins. CT imaging was used to determine spatial and air volume relationships of anatomic features. Regional blood flow was measured using ^{99m}Tc-bicistate SPECT in the heads of 2 dolphins, and the relative metabolic activity of head tissues was imaged using ^{18}F-FDG PET in 1 dolphin. The researchers noted substantial blood flow across the dorsoanterior curva-

ture of the melon (forehead) and within the posterior region of the lower jaw fats, but metabolism in these areas was quite low. This suggests that blood flow in these fat bodies serves to thermoregulate the lipid density of the melon and jaw canal, with changes in lipid temperature affecting the wave guide properties of the sound projection and reception pathways. They concluded that this unusual use of nuclear medicine tools showed that, "thermoregulation of lipid density may maintain sound velocity gradients of the acoustic lipid complexes, particularly in the outer shell of the melon, which otherwise might vary in response to changing environmental temperatures."

Journal of Experimental Biology

Treatment

^{90}Y-Labeled Diabodies Inhibit Tumor Growth

Adams et al. from the Fox Chase Cancer Center (Philadelphia, PA) reported in the September 1 issue of *Cancer Research* (2004;64:6200–6206) on promising results using ^{90}Y-labeled antitumor diabody molecules in radioimmunotherapy of human tumor breast xenografts in a mouse model. At about one third the size of monoclonal antibodies, diabodies are better able to penetrate tumors with relevant antigens and clear more rapidly from the circulation with greatly enhanced tumor-to-blood ratios. The authors conjugated ^{90}Y to the C6.5K-A diabody that targets the HER2/neu human tumor-associated antigen. A single intravenous dose of 150 μCi ^{90}Y-CHX-A″-C6.5K-A diabody substantially inhibited growth rates of established MDA-361/DYT2 human breast tumor xenografts in athymic nude mice. However, a similar 300-μCi injection resulted in only a minor delay in the growth of SK-OV-3 human ovarian cancer xenografts in mice. The authors concluded that "these studies indicate that genetically engineered antitumor diabody molecules can be used as effective vehicles for radioimmunotherapy." As a result of follow-up studies that found renal function impairment in some mice at 1 year after the injections, the researchers are now looking at the same diabody labeled with α-emitters

Cancer Research

Long-Term Follow-Up to ^{131}I in Graves Disease

Researchers from the University of Iowa reported in the September issue of the *Journal of Clinical Endocrinology and Metabolism* (2004; 89:4229–4233) on outcomes for patients treated with radioiodine for Graves disease between 1953 and 1973. The study by Read et al. included 107 former patients who were contacted by phone and e-mail and whose physicians supplied additional information about treatment. The group was surveyed first in 1991 and 1992 and again a decade later, when 98 former patients participated. At the time of treatment, the patients' ages ranged from 3 to 19 years. The average length of follow-up in 1991–1992 was 26.1 years and that in 2001–2002 was 36.2 years. Over the course of the decades since treatment, all except 2 of the patients became hypothyroid. None, however, developed cancer of the thyroid or leukemia. The authors concluded that, "Treating young people with Graves' disease with radioiodine is safe and effective over the long term."

Journal of Clinical Endocrinology and Metabolism

Propylthiouracil Before ^{131}I Therapy

Bonnema et al. from the Odense University Hospital (Denmark) reported in the September issue of the *Journal of Clinical Endocrinology and Metabolism* (2004;89:4439–4444) on the results of a clinical trial performed to clarify whether treatment with propylthiouracil (PTU) before ^{131}I therapy affects outcomes. The study included 23 hyperthyroid patients with Graves disease (n = 23) and 57 patients with toxic nodular goiter. Patients were randomized to pretreatment with PTU (n = 39) or no pretreatment (n = 41) before ^{131}I therapy. The median PTU dose was 100 mg, which was discontinued 4 days before treatment. At 1-year follow-up, the group with toxic nodular goiter who had received pretreatment showed an ^{131}I treatment failure rate 4 times higher than did those with no pretreatment. For patients with Graves disease, the difference was not statistically significant. All patients in the pretreated groups who were cured had higher serum thyroid stimulating hormone (TSH) levels at the time of ^{131}I therapy than those who were not cured. Statistical analysis showed that only PTU pretreatment had a significant adverse effect on the cure rate. The authors concluded that "PTU pretreatment reduces the cure rate of ^{131}I therapy in hyperthyroid diseases, although this adverse effect seems to be attenuated by the concomitant rise in serum TSH."

Journal of Clinical Endocrinology and Metabolism