

Each month the editor of *Newsline* selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.

PET/CT/MR and H&N Cancer Surveillance

Meerwein et al. from University Hospital Zurich (Switzerland) reported in the February 21 issue of the *Swiss Medical Weekly* (2015;145:w14116) on a retrospective study of ^{18}F -FDG uptake in head and neck cancers and nonmalignant lesions on PET/CT and MR imaging follow-up after treatment. The study included 87 patients (68 men, 19 women; ages, 24–90 y) undergoing follow-up (89.7%) or restaging (10.3%) PET/CT and MR imaging. Tumor recurrence or persistence was verified in 14 patients (16.1%), with a total of 159 nonmalignancy-associated PET-positive lesions identified (average of 2.1 ± 1.5 ^{18}F -FDG-positive lesions per PET/CT + MR examination). In 73 of 87 patients (83.9%) imaging and clinical follow-up showed no tumor persistence, recurrence, or soft-tissue metastases. The causes of the subset of nonmalignant tracer-positive lesions found in these patients were categorized as physiologic (107, 67.3%), 52 (32.7%) as inflammatory (14 postsurgical [8.8%], 9 as postradiation [5.7%], and 29 as reactive, not otherwise specified [18.2%]). Eight of the 73 patients underwent additional diagnostic procedures (biopsies, fine-needle aspiration)

to clarify indistinct findings. The authors noted that awareness of common confounders of ^{18}F -FDG positivity often allows clarification of indistinct lesions. However, “a substantial number of approximately 12% of FDG-positive lesions remain unclear unless invasive diagnostic procedures are performed.”

Swiss Medical Weekly

PET/CT in HNSCC

In a study published in the March 1 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2015;91:472–479), Anderson et al. from the University of Iowa (Iowa City) reported on a methodology using ^{18}F -FDG uptake on PET/CT for postradiotherapy assessment in differentiating inflammation from tumor in head and neck squamous cell carcinoma. The study included 84 such patients with 79 primary and 43 nodal evaluable sites, who underwent scheduled 3-mo posttherapy PET/CT imaging, including a whole-body scan at 90 min and additional head and neck scans at 60 and 120 min. A total of 28 sites were positive or equivocal (18 primary, 8 nodal, 2 distant) on whole-body PET/CT. Maximum standardized uptake values (SUV_{max}) in specified regions of interest were assessed at all 3 time points. The SUV_{max} slope between the 60- and 120-min time points was calculated, as was the change in SUV_{max} slope over the course of imaging. Imaging results were compared with histologic and clinical outcomes over a median follow-up of 13.3 mo. All measured SUV endpoints predicted recurrence, and the change in SUV_{max} slope after 90 min more accurately identified nonrecurrence in positive or equivocal sites than did the authors' current standard of $\text{SUV}_{\text{max}} \geq 2.5$. They concluded that “the positive predictive value of postradiotherapy FDG PET/CT may significantly improve using novel second derivative analysis of dynamic triphasic FDG PET/CT SUV_{max} slope, accurately

distinguishing tumor from inflammation on positive and equivocal scans.”

International Journal of Radiation Oncology, Biology, Physics

Pretreatment PET/CT in NSCLC

Ohri, from the Montefiore Medical Center/Albert Einstein College of Medicine (Bronx, NY), with the investigators of the American College of Radiology Imaging Network 6668/Radiation Therapy Oncology Group 0235, reported on February 16 ahead of print in the *Journal of the National Cancer Institute* on results of a trial assessing the prognostic value of volumetric pretreatment ^{18}F -FDG PET in non-small cell lung cancer (NSCLC). A total of 214 patients with stage III NSCLC underwent ^{18}F -FDG PET imaging before definitive and concurrent platinum-based chemoradiotherapy for locally advanced disease. All visible hypermetabolic lesions on each scan were contoured, and maximum standardized uptake values (SUV_{max}), metabolic tumor volume, and total glycolytic activity were recorded for all such lesions. Patients were followed for 12 months or more, with overall survival data available on all patients and locoregional control data available in 189. Metabolic tumor volume was found to be an independent predictor of overall survival in multivariate analyses, with high metabolic tumor volume also associated with increased risk of locoregional failure at baseline and 6 mo but not at 12-mo or longer follow-up. The authors concluded that “pretreatment metabolic tumor volume is a predictor of clinical outcomes for NSCLC patients treated with chemoradiotherapy” and that “quantitative PET measures may serve as stratification factors in clinical trials for this patient population and may help guide novel trial designs.”

Journal of the National Cancer Institute

PET/CT and RT Planning in Endometrial Cancer

In a study e-published on February 11 ahead of print in the *International*

Journal of Gynecological Cancer, Simcock et al. from the Peter MacCallum Cancer Centre (Melbourne, Australia) and the University of Otago (Christchurch, New Zealand) reported on the role of PET/CT in evaluating disease distribution as part of planning radiation therapy in endometrial cancer. The study included 73 women referred for adjuvant radiotherapy for endometrial cancer, with either high-risk disease after a hysterectomy or recurrent disease. All underwent PET/CT imaging before radiation treatment. PET/CT identified additional disease in 35% of the postoperative patients and changed planned treatment in 31%. These figures were 72% and 36% for patients in the group with known recurrence. The authors concluded that these results suggest that “PET/CT is a valuable tool for planning radiotherapy in endometrial cancer.”

International Journal of Gynecological Cancer

^{99m}Tc-Tilmanocept and Lymphatic Mapping in HNSCC

Agrawal, from The Ohio State University Wexner Medical Center (Columbus), and coinvestigators reported on February 11 ahead of print in the *Annals of Surgical Oncology* on a study evaluating the potential role of the CD206 receptor-targeted radiopharmaceutical ^{99m}Tc-tilmanocept (Lymphoseek; Navidea, Dublin, OH) in an open-label, phase III trial of sentinel lymph node biopsy (SLNB) in patients with intraoral or cutaneous head and neck squamous cell carcinoma (HNSCC). The study included 83 patients with T1–T4, N0, and M0 HNSCC scheduled to undergo tumor resection, SLNB, and planned elective neck dissection. Fifty micrograms of tilmanocept with either 0.5 mCi (same day) or 2.0 mCi (next day) ^{99m}Tc were administered, and patients proceeded to lymphoscintigraphy, SLNB, and elective neck dissection. Excised tissues were assessed for tissue type and tumor presence. ^{99m}Tc-tilmanocept identified ≥ 1 SLN in 81 of 83 patients (97.6%). Overall the results indicated a false-negative rate of 2.56% and a negative predictive value of 97.8%, with an

overall accuracy of 98.8%. No differences were noted between the same- and next-day administrations. The authors concluded that “receptor-targeted ^{99m}Tc-tilmanocept for lymphatic mapping allows for a high rate of SLN identification in patients with intraoral and cutaneous HNSCC,” accurately predicting pathologic nodal status in patients with intraoral cancers with low false-negative and high negative-predictive values, as well as high overall accuracy. They added that “the use of ^{99m}Tc-tilmanocept for SLNB in select patients may be appropriate and may obviate the need to perform more extensive procedures such as elective neck dissection.”

Annals of Surgical Oncology

PET/CT in CLL

In a study e-published on February 4 ahead of print in *Leukemia*, Mauro, from Sapienza University (Rome, Italy), and a consortium of researchers from Italy and France reported on a study designed to elucidate the diagnostic and prognostic roles of PET/CT in patients with chronic lymphocytic leukemia (CLL) and progressive disease. The authors reviewed retrospective data on 90 patients with CLL who underwent PET/CT and biopsy for suspicion of Richter syndrome or a second malignancy. Median maximum standardized uptake values (SUV_{max}) were 3.5 for CLL/small lymphocytic lymphoma, 14.6 for diffuse large B-cell lymphoma, 7.0 for Hodgkin lymphoma, and 6.3 for a second malignancy. An SUV_{max} cutoff value ≥ 5 showed sensitivity, specificity, and positive and negative predictive values of 88.2%, 71.2%, 51.3%, and 94%, respectively, for the presence of more aggressive disease. An SUV_{max} ≥ 5 also identified a subset of treatment-naïve patients with inferior progression-free and overall survival. The authors concluded that these findings “suggest that PET/CT may helpfully integrate the biologically based prognostic stratification of CLL,” although larger prospective clinical trials are needed.

Leukemia

Prognostic PET after R-CHOP in DLBCL

Song et al. from Pusan National University (Busan, Republic of Korea) reported on February 17 ahead of print in *Annals of Hematology* on a study investigating the prognostic role of ¹⁸F-FDG PET/CT after rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy in diffuse large B-cell lymphoma. The study included 270 patients with DLBCL who achieved complete response on PET/CT after R-CHOP therapy. PET/CT findings were used to categorize patients as with or without diffuse thyroid uptake after therapy, with a median time to diffuse thyroid uptake detection of 5.7 mo (range, 0–21.3 mo). Diffuse thyroid uptake was correlated with autoimmune thyroiditis in 61 patients. Factors significantly associated with progression-free and overall survival were found to be a high International Prognostic Index score, bulky mass ≥ 10 cm, bone marrow involvement, and diffuse thyroid uptake after R-CHOP therapy. Diffuse thyroid uptake after R-CHOP therapy independently predicted outcomes in DLBCL patients.

Annals of Hematology

PET in Diagnosis and Management of Anal Cancer

In a study e-published on February 5 ahead of print in *Annals of Surgical Oncology*, Jones et al. from the Royal Prince Alfred Hospital (Camperdown, Australia) provided a systematic review and metaanalysis comparing the role of ¹⁸F-FDG PET and PET/CT with that of conventional imaging in detection of primary and nodal disease in anal cancer and assessing the effects of PET or PET/CT on management. A review of the literature identified 12 studies for inclusion. These studies compared PET or PET/CT with conventional imaging in the staging of histologically confirmed anal squamous cell carcinoma (SCC) or in assessment of response to treatment. CT and PET had sensitivities of 60% and

99%, respectively, for detection of primary disease. PET led to a change in nodal staging in 28% of patients when compared to staging with conventional imaging. For PET/CT, TNM stage was changed by 78% when compared with conventional imaging. After chemoradiotherapy, 78% of patients in these studies showed complete responses on PET. The authors concluded that “compared with conventional imaging, PET or PET/CT alters the nodal status in a sufficient number of cases to justify its routine use in the staging of patients with anal SCC.”

Annals of Surgical Oncology

PET and Personalized Treatment in NSCLC

Toma-Dasu et al. from Stockholm University and Karolinska Institutet (Sweden), RaySearch Laboratories AB (Stockholm, Sweden), Maastricht University Medical Center (The Netherlands), and Linköping University (Sweden) reported in the February 1 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2015;91:376–384) on a study using ¹⁸F-FDG PET at 2 time points to assess early tumor response and effective radiosensitivity in patients with non-small cell lung cancer (NSCLC). The study included 26 patients with NSCLC, 15 of whom underwent sequential chemotherapy and radiation and 11 of whom underwent concurrent chemoradiation. Patients underwent ¹⁸F-FDG PET imaging before and 2 weeks after radiation therapy, with images analyzed in correlation with the dose of radiation delivered. Patients were then followed for up to 2 years to identify correlations between the average effective radiosensitivity and overall survival. The researchers were able to categorize patients receiving sequential treatment as responders or nonresponders, based on a threshold of average effective radiosensitivity of 0.003 Gy⁻¹ in the primary gross target volume, with a sensitivity of 75% and a specificity of 100%. The authors concluded that the proposed methodology for evaluation of early response in NSCLC “has potential to identify candidates for more aggressive

strategies to increase the rate of local control and also avoid exposing to unnecessary aggressive therapies the majority of patients responding to standard treatment.”

International Journal of Radiation Oncology, Biology, Physics

PET/CT and MR in Nodal Staging in Prostate Cancer

In an article published on February 2 ahead of print in *Urologic Oncology*, Van den Bergh et al. from Katholieke Universiteit Leuven (Belgium) reported on a study assessing the sensitivity, specificity, and positive and negative predictive values of ¹¹C-choline PET/CT and diffusion-weighted MR imaging for nodal staging in patients with prostate cancer at high risk for lymph node involvement. The study included 75 men with a 10%–35% risk of lymph node metastases (using Partin table criteria) with no regional lymph node involvement on contrast-enhanced CT. All patients underwent ¹¹C-choline PET/CT and diffusion-weighted MR imaging before proceeding to superextended lymph node dissection and radical prostatectomy. Histologic results from resected lymph nodes were compared with imaging results. Out of a total of 1,665 resected lymph nodes, 106 (median, 2/patient; range, 1–10/patient) were identified in 37 of the 75 patients (49%). Region-based analyses indicated that PET/CT had a low sensitivity of 8.2% and a positive predictive value of 50%. The respective percentages were 9.5% and 40.0% for MR imaging. Patient-based analyses indicated that PET/CT had a low sensitivity of 18.9% and a positive predictive value of 63.6%. The respective percentages for MR imaging were 36.1% and 86.7%. Combining data from the 2 modalities failed to raise sensitivity levels to the range needed for clinical utility. The authors concluded that “because of the low sensitivity, there is no indication for routine clinical use of either ¹¹C-choline PET/CT or diffusion-weighted MRI for lymph node staging in patients with prostate cancer, in whom CT scan findings were normal.”

Urologic Oncology

²⁰¹Tl SPECT vs ¹⁸F-FDG PET in Meningiomas

Okuchi et al. from the Kyoto University Graduate School of Medicine (Japan) reported in the February issue of *Medicine (Baltimore)* (2015;94:e549) on a retrospective comparison of ²⁰¹Tl SPECT and ¹⁸F-FDG PET in grading of meningiomas. The study included 67 patients (22 men, 45 women) with diagnoses of meningioma confirmed by histopathology who underwent both ²⁰¹Tl SPECT and ¹⁸F-FDG PET before surgery. Uptake values were measured on PET and standardized to whole-body (SUV_{max}) and normalized as gray matter ratios (SUVR_{max}). Maximum and mean ²⁰¹Tl uptake ratios of tumors were normalized as ratios to those of the contralateral normal brain. A total of 56 meningiomas were classified as low grade and 11 were classified as grade II or III (high grade) using receiver-operating characteristic curve analyses. For all 4 of the uptake characteristics assessed, significant differences between low- and high-grade meningiomas were observed. Areas under the curve were 0.817 for SUV_{max}, 0.781 for SUVR_{max}, 0.810 for mean ²⁰¹Tl uptake, and 0.831 for maximum ²⁰¹Tl uptake. The sensitivities of the 2 imaging techniques were high and comparable. The authors concluded that ²⁰¹Tl SPECT, “which can be used at hospitals without a cyclotron or an FDG distribution network, has high diagnostic capability of meningioma grades comparable to FDG PET.”

Medicine (Baltimore)

¹¹C-Met PET/CT in Parathyroid Adenomas

In an article e-published on February 10 ahead of print in the *World Journal of Surgery*, Lenschow et al. from the University Hospital of Muenster (Germany) reported on a study designed to determine whether the addition of ¹¹C-methionine PET/CT increases precise localization of parathyroid adenomas and thereby increases the number of focused parathyroidectomies. The study included 14 patients with primary hyperparathyroidism and 3 with

tertiary hyperparathyroidism who underwent cervical ultrasonography and ^{99m}Tc -MIBI SPECT/CT. Those with negative SPECT results underwent ^{11}C -methionine PET/CT, with subsequent surgical management changes based on imaging. A single parathyroid adenoma was localized by ultrasound in each of 10 patients (59%), and ^{99m}Tc -MIBI SPECT/CT localized 1 in each of 11 patients (65%). ^{11}C -methionine PET/CT identified 5 single parathyroid adenomas in the remaining 4 patients, resulting in identification of single adenomas in 94% of patients. The authors concluded that ^{11}C -methionine PET/CT “raises the rate of correctly localized single parathyroid adenomas in patients with negative cervical ultrasonography and ^{99m}Tc -MIBI SPECT/CT and increases the number of focused surgical approaches.”

World Journal of Surgery

Brain Structure, Function, Amyloid, and Memory

Mattsson, from the Department of Veterans Affairs Medical Center (San Francisco, CA), and a large number of coauthors from California and Sweden reported on February 13 ahead of print in *Neurology* on a study designed to determine whether the effects of β -amyloid ($\text{A}\beta$) pathology on episodic memory are mediated by metabolism and gray matter volume in early-stage Alzheimer disease (AD). The cohort study included 743 participants (280 cognitively healthy controls, 463 with mild cognitive impairment [MCI]). Each participant underwent ^{18}F -florbetapir PET, ^{18}F -FDG PET, and MR imaging, to assess baseline $\text{A}\beta$, brain function, and brain structure, respectively. Analyses were performed to determine whether the statistical effects of $\text{A}\beta$ positivity on cross-sectional and longitudinal episodic memory were affected by hypometabolism or regional gray matter volume. The authors found that lower memory scores were mildly associated with $\text{A}\beta$ positivity in healthy controls and strongly associated in MCI. Lower memory scores were also associated with smaller gray matter volumes and hypometabolism. Smaller gray matter

volumes and hypometabolism were found to mediate the effects of $\text{A}\beta$ in MCI but not in healthy controls. A combination of brain structure and function were found to mediate up to 40% of effects in MCI. However, in several regions, gray matter atrophy and hypometabolism predicted episodic memory but were not associated with $\text{A}\beta$ positivity. The authors concluded that “changes in brain structure and function appear to be, in part, downstream events from $\text{A}\beta$ pathology, ultimately resulting in episodic memory deficits.” They cautioned that these imaging assessments do not capture all of the mechanisms through which $\text{A}\beta$ pathology is associated with memory deficit and that episodic memory decline is caused, in part, by AD-like brain changes that are independent of $\text{A}\beta$ pathology.

Neurology

Prevalence and Prognosis of AD in MCI

In an article e-published on February 17 ahead of print in *Brain*, Vos, from Maastricht University (The Netherlands), and a consortium of more than 30 researchers from The Netherlands, Germany, Italy, France, the UK, Finland, Poland, Greece, Belgium, Portugal, and Sweden used 3 sets of widely recognized criteria for diagnosis of Alzheimer disease (AD) to compare the prevalence of and prognosis for AD at the mild cognitive impairment (MCI) stage. The 3 established criteria were those of the International Working Group 1, International Working Group 2, and the National Institute of Aging–Alzheimer Association criteria. The study included 1,607 (766 with both amyloid and neuronal injury markers) individuals with MCI. Using the International Working Group 1 criteria, 850 individuals (53%) had prodromal AD, with a 3-y progression rate to AD-type dementia of 50% compared to only 21% without prodromal disease. Using the International Working Group 2 criteria, 308 individuals (40%) had prodromal AD, with a 3-y progression rate to AD-type dementia of 61% compared to 22% without prodromal AD.

Using the National Institute of Aging–Alzheimer Association criteria, 353 individuals (46%) were in the high AD likelihood group, 49 (6%) in the isolated amyloid pathology group, 220 (29%) in the suspected non-AD pathophysiology group, and 144 (19%) in the low AD likelihood group. The 3-year progression rates to AD-type dementia were 59% in the high AD likelihood group, 22% in the isolated amyloid pathology group, 24% in the suspected non-AD pathophysiology group, and 5% in the low AD likelihood group. The authors concluded that these findings “support the use of the proposed research criteria to identify AD at the MCI stage.” They noted that in clinical settings, the inclusion of both amyloid and neuronal injury markers as in the National Institute of Aging–Alzheimer Association criteria offers the most accurate prognosis, whereas in clinical trials, selection of subjects in the National Institute of Aging–Alzheimer Association–designated high AD-likelihood group or the International Working Group 2 prodromal AD group could be considered.

Brain

Postoperative ^{18}F -FDG PET in DTC

Nascimento et al. from the Gustave Roussy Institute (Villejuif, France) and the Institut Curie (Saint-Cloud, France) reported on January 29 ahead of print in *Thyroid* on a study evaluating the sensitivity of postoperative ^{18}F -FDG PET/CT in differentiated thyroid cancer (DTC) and identifying risk factors for abnormal imaging findings in this setting. The retrospective study included 38 patients (16 men, 22 women; mean age, 57 y) with DTC with aggressive histology (tall cell papillary carcinoma, 45%; poorly differentiated carcinoma, 42%; others, 13%) but without known persistent disease at the time of postoperative ^{131}I ablation. All patients underwent post-ablation ^{18}F -FDG PET/CT and whole-body ^{131}I imaging. A total of 86 lesions were identified in 20 (53%) patients, distributed in 33 organs. PET/CT and the whole-body scan indicated persistent

disease in 15 and 12 patients, respectively, with PET/CT more sensitive than whole-body imaging for detection of individual lesions (69% and 59%, respectively). The imaging techniques were complementary, with 41% of lesions detected only by PET/CT and 31% only by whole-body scanning. Thyroglobulin levels measured at ablation were found to correlate positively with abnormal PET/CT imaging. The authors concluded that “postoperative FDG-PET/CT should be routinely performed in patients with aggressive histology DTC.”

Thyroid

Glutamine-Based PET and Gliomas

In an article published in the February issue of *Science Translational Medicine* (2015;7:274ra17) Venneti, from the University of Michigan (Ann Arbor), and researchers from the Memorial Sloan Kettering Cancer Center (New York), the University of Pennsylvania (Philadelphia), and the University of Washington (Seattle) reported on a study designed to determine whether a glutamine-based analog for PET imaging can resolve challenges associated with glucose-based ^{18}F -FDG PET in gliomas, where brain background uptake is challenging. In animal studies, the authors showed that the glutamine analog 4- ^{18}F -(2S,4R)-fluoroglutamine (^{18}F -FGln) had high uptake in gliomas but low background brain uptake, allowing for clear tumor delineation. Chemoradiation in small animal glioma models reduced

^{18}F -FGln tumor uptake consistently with decreased tumor burden. They noted that uptake of the radiolabeled glutamine analog was not seen in animals with neuroinflammation or a permeable blood-brain barrier. In initial human studies in patients with gliomas and progressive disease, ^{18}F -FGln showed high tumor-to-background ratios with minimal uptake in surrounding brain. The authors concluded that these data “suggest that ^{18}F -FGln is avidly taken up by gliomas, can be used to assess metabolic nutrient uptake in gliomas in vivo, and may serve as a valuable tool in the clinical management of gliomas.”

Science Translational Medicine

Reviews

Review articles provide an important way to stay up to date on the latest topics and approaches by offering valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in January and February 2015. In an article e-published in the April issue of *Current Cardiology Reports* (2015;17:572), Ayoub et al. from the University of Ottawa Heart Institute (Canada) described “Advanced imaging of cardiac sarcoidosis.” Asman et al. from the Tel Aviv Medical Center and Tel Aviv University (Israel) outlined the utility of “ ^{18}F -FDG PET-CT as a prognostic tool prior to liver transplantation, resection, and loco-ablative therapies for hepatocellular carcinoma” on January 31 ahead of

print in *Liver Transplantation*. In a review e-published on January 28 in *BioMed Research International*, Ripa and Kjaer from the Rigshospitalet and University of Copenhagen (Denmark) reported on “Imaging atherosclerosis with hybrid positron emission tomography/magnetic resonance imaging.” Schmidt et al. from the University of Heidelberg, University Hospital Leipzig, University Hospital Würzburg, and the RoMed Klinikum Rosenheim (all in Germany) provided an overview of the “Value of functional imaging by PET in esophageal cancer” in the February issue of the *Journal of the National Comprehensive Cancer Network* (2015;13:239–247). In an article e-published on February 12 in *Neuroscience and Behavioral Reviews*, Zürcher et al. from the Massachusetts General Hospital and the Harvard Medical School (Boston, MA) authored “A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities.” Van den Berghe and Marsden from Ghent University (Belgium) published “PET-MRI: a review of challenges and solutions in the development of integrated multimodality imaging” in the February 21 issue of *Physics in Medicine and Biology* (2015;60:R115–R154). In a review e-published on February 11 ahead of print in the *Journal of Medicinal Chemistry*, Ariza et al. from Janssen Research and Development (Beerse, Belgium) described “Tau PET imaging: past, present, and future.”

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