Stunning After Tracer Dosimetry

TO THE EDITOR: We read with interest the article by Yeung et al. (*1*) on therapeutic radioiodine uptake in thyroid remnants after tracer dosimetry. The authors reported decreased uptake in thyroid remnants if ^{131}I-based dosimetry preceded therapy. Unlike other studies (*2–5*) in which a threshold of 111 MBq ^{131}I was observed before thyroid stunning occurred, the authors reported decreased iodine uptake even with doses as low as 37 MBq ^{131}I.

We congratulate the authors on their excellent study. However, we cannot fully agree with their conclusion that the thyroid stunning was caused by radiation damage from the dosimetric tracer dose. Assuming the effect of thyroid stunning, one would expect a correlation between the amount of radioiodine in remnant tissue (diagnostic dose × diagnostic uptake) and the degree of stunning (ratio of diagnostic uptake to therapeutic uptake). This correlation cannot be found in the data presented in the study ($r = -0.08$).

With respect to this lack of correlation, we believe instead that there is considerable intratherapeutic stunning rather than dosimetric stunning. Within the first hours after therapeutic radioiodine administration, high radiation doses within thyroid remnant tissue can be expected to have major influence on the subsequent iodine clearance rate in the remnant tissue (iodine subsequently taken up in the stomach and radioiodine coming from the liver after deiodination of radioactive thyroid hormones). This theory would also agree with the previous studies that reported a higher threshold for dosimetric doses.

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REPLY: As we stated in our article (*1*), we expected a correlation between the radiation dose to the remnant and the ratio of diagnostic uptake to therapeutic uptake (the stunning effect). However, the radiation dose depends on both the amount of radioiodine in remnant tissue and on the tissue mass, which in most cases is not known. Hence, when the diagnostic uptake is low, the radiation dose may be high if the tissue mass is very low. This phenomenon may explain the lack of correlation between the amount of radioiodine in remnant tissue and the stunning effect.

The possibility of intratherapeutic stunning is a good point that we cannot address with our data. We would need to scan the patient at multiple time points after administration of the therapeutic dose. If the hypothesis of Drs. Diehl and Grünwald were correct, then the ^{131}I clearance from the lesion would be faster. Incidentally, if intratherapeutic stunning occurs, performing dosimetry with ^{123}I would also show a reduction in uptake of ^{131}I from the therapeutic administration.

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Thyroid Stunning

TO THE EDITOR: Recently, 2 articles (*1,2*) on thyroid stunning have been published in *The Journal of Nuclear Medicine*. Yeung et al. (*1*) quantitatively confirmed significantly lower uptake of therapeutic ^{131}I in the neck after diagnostic imaging with low activity of ^{131}I (*3*) and presented evidence of thyroid stunning even after the diagnostic administration of ≤40 MBq ^{131}I. Cholewinski et al. (*2*) found no visually apparent post-therapeutic thyroid stunning after diagnostic scintigraphy with 185 MBq ^{131}I performed 3 d before radioiodine therapy.

Thyroid stunning is usually defined as decreased ability of normal thyroid or metastatic tissue to trap or retain therapeutic radioiodine, as a result of a previously administered diagnostic amount of ^{131}I. Such a definition implies that the effect is quantitative and that measurement of fractional lesion uptake must be taken. Visual assessment of scintigraphic changes in thyroid remnants or cancer kinetics of radioiodine cannot be objective in every respect. Visualizing the same number of foci and the same relative intensity of uptake (*2*) does not prove the absence of stunning, because the ratio of observed uptake to predicted uptake can still be lower than the ratio of administered therapeutic activity to diagnostic activity. As a rule, quantitative studies on thyroid stunning have found decreased efficacy per unit of therapeutic activity of ^{131}I after the diagnostic administration of ^{131}I (*1,3–5*), whereas visual assessment has often failed to recognize it (*2*). Furthermore, radiation absorbed dose (Gy) and dose rate (Gy/h) are the parameters that most clearly explain the impact of ionizing radiation on living organisms, though consideration of these 2 parameters is usually neglected.

It is to be regretted that both recent papers (*1,2*) failed to refer to the work of Jeevanram et al. (*4*), which to our knowledge is the only article in the literature that considers the influence of the diagnostic absorbed dose of ^{131}I on the subsequent therapeutic uptake of ^{131}I. In their article, Jeevanram et al. (*4*) showed that the higher the diagnostic absorbed dose, the higher the reduction of therapeutic uptake of ^{131}I will be. In their study, the mean therapeutic uptake at 72 h was only about one half of the diagnostically expected uptake, whereas the diagnostic absorbed dose of up to 17.5 Gy appeared as a dose level of acceptably negative influence with, on average, 24% reduced therapeutic uptake (*4*).

After surgery on our patients for well-differentiated thyroid cancer, we calculated both the diagnostic and the therapeutic

absorbed doses on the basis of determined functional mass of the target organ and the integration of the time–activity curves, which were constructed from serial uptake measurements (*5*). The mean therapeutic absorbed dose was only about one half of the value predicted by a work-up study with 75 MBq ^{131}I (*5*). The correlation between the diagnostic absorbed dose and the reduction of therapeutic absorbed dose was clear, whereas the diagnostic absorbed dose above which thyroid stunning becomes significant was found to be 10 Gy (*5*).

We believe that any future quantitative investigation of diagnostic and therapeutic kinetics of radioiodine should take into consideration 2 points. First, different diagnostic and therapeutic fractional lesion uptake at a specific time point may result from different shapes of the retention curves (different maximums, different half-lives). Therefore, single measurements of the uptake at the same time after administration of diagnostic and therapeutic radioiodine are indicative (*1,3,4*) but not conclusive. For a more reliable comparison of activity retention, as many measurements should be taken as possible. Second, different diagnostic and therapeutic fractional lesion uptake may result from changes in lesion mass as a function of time. Potential loss or gain of the lesion mass during the study (radiation damage, thyroptin stimulation) may change the absolute amount of the activity in the lesion, even if the uptake per gram of the target tissue remains constant.

We made a few other noteworthy observations regarding the 2 recent papers. In Yeung et al. (*1*), Figure 2 shows the correlation ($r = 0.75$; slope = 0.42) between percentage uptake of diagnostic and therapeutic activity (*1*); it is obvious that the uptake of patient 2 (listed in Table 1) is not present on the graph, whereas the slope of the regression line is much greater than 0.42. Recalculation in both lesion-to-lesion and patient-to-patient cases gives very good correlation between diagnostic and therapeutic uptake ($r = 0.95$; $P < 0.01$; slope ≥ 0.83). Furthermore, excluding the most outlying point (patient 3) from the plot on Figure 3 makes the correlation between the ratio of therapeutic to diagnostic uptake (%T/D) and diagnostic activity significant ($r = -0.72$; $P < 0.02$). Thus, it seems that the stated unpredictability of the degree of stunning (*1*) does not hold, as has been reported previously (*3,4,5*).

In Cholewinski et al. (*2*), the camera tracking speed was 10–12 cm/min for diagnostic whole-body scans and 20 cm/min for post-therapeutic whole-body scans, and the administered diagnostic and therapeutic activities were 185 and 5,550 MBq ^{131}I, respectively. Assuming similar diagnostic and therapeutic retention of radioiodine, visual comparison of 2 scintigrams for stunning with counting statistics different for an order of magnitude would be difficult. Nevertheless, on Figure 1, which should show no evidence of stunning by the diagnostic dose (*2*), the lesions in the thyroid bed appear scintigraphically less prominent on the therapeutic than on the diagnostic scan, and ^{131}I concentration in the left shoulder was not mentioned at all.

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REPLY: At Memorial Sloan-Kettering Cancer Center (New York, New York), we annually perform about 200 thyroid dosimetry studies. In these studies, patients are usually administered a tracer dose of 37–185 MBq ^{131}I, primarily to determine the maximum tolerated dose, which is defined as that activity that would result in a radiation absorbed dose of 2 Gy to blood (*1,2*). These patients receive serial whole-body gamma camera scanning on days 1, 2, and 4 and daily neck uptake measurements using a neck probe. Radiation absorbed dose to the tumor is estimated in these patients. However, the accuracy of these estimates depends on the mass of the lesion, which is rarely known, particularly because the tumors for many of our patients are either at or below the limits of the resolution of the gamma camera. In such instances, even CT is not a reliable estimator of tumor mass. For this purpose, we are investigating the potential of PET using ^{124}I with the hope of improving tumor dose quantitation (*3*). The initial intention of the study was to correlate the magnitude of stunning with the absorbed dose from the dosimetry study before therapy, but we discovered that this was not possible in these patients.

We have recalculated the slope and correlation coefficient for the plot of percentage uptake from the therapy scan versus percentage uptake from the dosimetry scan (Fig. 2 (*4*)). The original Figure 2 was incorrect and the recalculated slope was 0.78 with an R^2 of 0.89, which suggests a much better correlation than previously presented. However, this is a trend line with a large scatter of points around the line of best fit.

When the percentage uptake of the therapeutic dose relative to the diagnostic dose (%T/D) was plotted against the administered activity, no correlation was found ($R^2 = 0.001$). With no stunning, all data points should lie along a horizontal line at 100%. If stunning is correlated with the amount of radioiodine administered, a progressive reduction in %T/D would be expected. One point at 388% can definitely be considered an outlier by the Thompson criterion (*5*). A re-estimation of the correlation coefficient with this data point omitted resulted in little improvement in the correlation coefficient ($R^2 = 0.0643$).

These data reveal nothing about the magnitude of stunning versus radiation absorbed dose. We agree with Dr. Medvedec that a dependence of the degree of stunning on the radiation dose is to be expected. We expected it too but were unable to show it in our work. However, other factors that will also impact the magnitude of stunning should not be neglected. First, the amount of radioiodine accumulation will depend on the tumor histology, with stunning conjectured to be greater in a well-differentiated tumor with a more intact follicular histology. Second, in 1 patient with 2 neck lesions (patient 10 in our study (*4*)) of possibly different histologic type, we observed that the uptake in one lesion was greatly reduced during the therapy, with a concomitant increase in the second lesion of lower percentage uptake on the dosimetry scan. This was presumably a consequence of competition; that is, the first lesion acted as an iodine sink for the second lesion during the dosimetry

scan but exhibited greater uptake once the radiation effects had damaged the trapping of the first lesion.

In conclusion, we generally agree with the remarks made by Dr. Medvedec. Although we did not observe a strong correlation between administered activity and the magnitude of stunning, we do anticipate an improved correlation when correlated with lesion dose, with the reminder that there are several other factors such as histologic type that will also impact the magnitude of the effect.

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REPLY: We read with attention Dr. Medvedec's Letter to the Editor, which raises several interesting points.

Thyroid stunning implies lower uptake of the therapeutic dose than that expected from the diagnostic dose; its importance lies in its potential effect in reducing the efficacy of ^{131}I therapy. The purpose of our study was to try to evaluate whether decreased uptake, should it exist and be sufficient to suggest reduced therapeutic efficacy, was evident in our studies. Our data suggest that this is not the case, as evidenced by our patient population's long-term survival rates, which compare favorably with those of other centers.

We intentionally chose to analyze the data visually rather than by semiquantitative approaches used by other colleagues for several reasons. These semiquantitative approaches fail to take into account several important factors that affect the results. For example, the thyroid remnant is not the only organ to which ^{131}I is distributed. Therefore, a therapeutic dose of ^{131}I may not be distributed to all the organs in the same proportion as a diagnostic dose, because of nonlinear variation in rates of transfer between different compartments. Furthermore, we feel it would be overly simplistic to conclude that the fractional uptake of the therapeutic dose was reduced by the diagnostic dose merely because a region-of-interest ratio or a similar index was reduced. Hence, a conclusion of "decreased efficacy per unit therapeutic activity" would be vague and should be regarded as a possibility rather than as proven fact unless it is supported by other data, by visual or long-term follow-up, or by a similar parameter that actually demonstrates the detrimental consequences. If the numbers show a significantly large reduction that is neither visible in the images to a trained professional nor shown to affect the long-term efficacy of treatment and prognosis of a patient, then we respectfully suggest that the scientific process demands that we re-examine and refine the process generating those numbers, that is, modifying the theory to fit the facts rather than the reverse.

In view of this statement, we do not believe that a difference in tracking speed between the diagnostic and therapeutic scans or the range of ^{131}I doses affects our conclusions. We saw the same number of lesions, with similar relative intensities in all our patients, in both sets of images. If the severity of stunning is as high as 40%–50% in certain cases, as suggested by some quantitative parameters, one would not expect to see a residual focus or metastatic lesion in a therapeutic scan that had been seen on a diagnostic study, which would suggest that it may not have been adequately treated. Of course, in this scenario, one must then also show that the lesion subsequently grew bigger to the detriment of the patient, requiring active management.

We would like to point out that the apparent difference in the thyroid bed lesion in our Figure 1 (*1*) is caused by slightly different thresholding of the exposed film rather than by any significant difference in uptake, as is borne out by the relative intensity of the gut between Figures 1A and 1B. However, we agree that the caption omits the metastatic lesions in the left shoulder and the right lung; our intention was to point out a metastatic lesion in addition to the thyroid bed as an example in this patient's case. Indeed, both of the lesions not mentioned in the caption are seen at a similar relative intensity in both images, further supporting our conclusions about the lack of visually apparent stunning.

We regret that we did not refer to Jeevanram et al. (*2*) in our article. We derived our list of references from a computerized Medline search, which we assumed to be complete for our search keywords. However, our previous comments also apply to the methodology of this article as well.

We thank the authors for their interest in the subject and in our article.

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SPECT Imaging in Dementias

TO THE EDITOR: We wish to comment on certain aspects of an interesting recent paper by Hoffman et al. (*1*).

In initial evaluation of new patients who might be suffering from one of the dementias, it is common practice in many institutions to obtain an MRI scan of the head, largely to rule out various organic lesions such as stroke or neoplasms; furthermore, occasionally changes in the hippocampi and inferior medial temporal cortical regions may indicate early Alzheimer's disease (AD). However, in several AD clinics, MRI has been supplemented by a second examination intended to evaluate certain aspects of brain physiologic function. Hoffman et al. (*1*) make a case for the use of ^{18}F-FDG PET. In assessing alternatives to PET

involving radionuclide imaging, Hoffman et al. consider several studies performed with SPECT and a variety of regional cerebral blood flow (rCBF) tracers. One of these was the first report from our group on histopathologically confirmed prospective SPECT diagnoses in 18 patients, in which we examined certain features of rCBF SPECT for its efficacy in the diagnosis of AD (*2*). Unfortunately, the authors missed our following report (*3*), in which we described our results in 54 patients, also with histopathologic confirmation. To assist readers in evaluating the role of SPECT in the study of patients with AD and other dementias, we thought that it might be useful to review our more recent SPECT results.

We performed SPECT rCBF scans on 504 patients with possible dementia and 32 elderly healthy volunteers (age range, 56–89). The first half of our experience involved the use of inhaled ^{133}Xe and an appropriate 4-detector scanner, while the most recent 254 studies were done with ^{99m}Tc-hexamethylpropyleneamine oxime and a triple-camera scanner. Histopathologic correlation with prospective diagnoses for the presence or absence of AD was obtained in 79 patients, with the following results: sensitivity = 53/61 (86.9%; 95% confidence limits [CL], 75.2%–93.8%); specificity = 13/18 (72.2%; CL, 46.4%–89.3%); positive predictive value = 53/59 (89.8%; CL, 78.5%–95.8%); and negative predictive value = 13/20 (65.0%; CL, 40.9%–83.7%).

Of the 79 diagnoses, 77 were made at autopsy, 1 was made by both biopsy and subsequent autopsy, and 1 by biopsy alone. We compared the sensitivity of each of the tracers for the diagnosis of AD and find that they do not differ significantly ($P = 0.29$, 2-tailed Fisher exact test) (*3*).

In our series, the interval between initial prospective diagnosis and histopathologic correlation had a mean of approximately 48 mo, which is to be expected when patient survival occasionally exceeds 10 y after initial SPECT study. Hoffman et al. (*1*) are fortunate in having a somewhat shorter interval of 30.8 mo, but theirs is a small series of 22 patients; with an increasing number of patients, the mean length of time will increase as well, as will the extent of disease at autopsy and their chances of making false-negative diagnoses.

At the present time, our AD center's clinical staff has become adept at diagnosing typical AD even in its early stages; in these cases rCBF SPECT scans are no longer obtained. However, the staff frequently refers for SPECT patients whose symptoms and test results are confusing. The result often suggests one of the frontotemporal entities, which will become an important distinction if a specific treatment for AD becomes available. Lewy body disease, which is usually combined with AD, may also present a perplexing clinical aspect; 11 such cases have been referred for SPECT scans, and 10 have yielded true-positive SPECT results for AD. The presence of Lewy body disease may contribute an additional diagnostic sign in the form of abnormally reduced occipital cortical rCBF (*4*), which may occur in the absence of occipital cortical Lewy bodies at autopsy. However, one must keep in mind that reduced occipital cortical flow may also be seen in certain patients with depression but no dementia (*5*).

On the basis of our experience, we believe that because it is widely available and is less expensive than PET, rCBF SPECT, which performs well as a diagnostic test, might be combined with MRI as the experimental approach of choice for patients suspected of dementia whose clinical diagnosis is unclear.

ACKNOWLEDGMENTS

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REPLY: We appreciate the letter of Dr. Bonte et al. regarding our article (*1*). As the authors note, we did not cite their more recent publication (*2*), but we did acknowledge their first and very important study evaluating the use of brain blood flow in dementias using SPECT (*3*). Because of the limit on the number of references that could be cited, we chose to use the earlier publication by the authors because it was one of the first studies to use functional imaging techniques and histologic verification rather than clinical diagnosis in the evaluation of dementia. Dr. Bonte and his colleagues should be recognized for their contributions and pioneering work in the assessment of dementia with functional imaging techniques and their correlation of imaging results with pathologic diagnoses rather than clinical diagnoses.

Dr. Bonte and his colleagues now provide data on 79 patients who have had both pathologic verification of diagnosis and SPECT regional cerebral blood flow (rCBF) imaging. These new data confirm the results of their previous work with SPECT, showing a sensitivity for the diagnosis of Alzheimer's disease (AD) at approximately 87%, a specificity of 72%, and a calculated accuracy of 83.5%. These values are very similar to the values we determined for ^{18}F-FDG PET in our publication.

An important fact to keep in mind is the purpose of our study. We were specifically interested in confirming, with pathological verification, the data in the literature that bilateral temporoparietal hypometabolism using FDG PET is the metabolic abnormality associated with Alzheimer's disease. We also wanted to determine that the sensitivity, specificity, and diagnostic accuracy of the metabolic pattern of bilateral temporoparietal hypometabolism allows for differentiation between AD and other degenerative causes of dementia. These major goals of our study were satisfied.

Both articles by Bonte et al. (*2*,*3*) as well as our article (*1*) note the difficulties of evaluating dementia with metabolic and functional assessments, particularly regarding confounding pathologic diagnoses. The coexistence of Lewy body disease, vascular dis-

ease, or other degenerative processes with AD clearly is one source of confusing diagnosis that must be considered. This possibility for a coexisting disease was another concern in our study and part of why a unilateral reduction in FDG uptake was not considered as a hallmark for the diagnosis of AD. Unilateral reductions may well favor the metabolic correlate of a remote vascular event or a disease process other than AD.

There are also differences in approaches to image interpretation and analysis between our study and those of Bonte et al., which might possibly affect sensitivity, specificity, and accuracy calculations. In their more recent article, the sensitivity for visual interpretation was not specifically given for the 54 patients in the study; however, imaging sensitivity using a combined visual and semiquantitative approach was 37/43 (86%) and the specificity was 8/11 (73%). The sensitivity results are essentially the same between their earlier and later studies, which is important in light of the increased number of patients. In their earlier report, both bilateral and unilateral perfusion changes were interpreted as positive for AD. In 37 of their true-positive cases, 22 were based on bilateral reductions in perfusion (22 true-positives and zero false-positives). In 15 of the 37 true-positive cases the AD diagnosis was based on a unilateral reduction (15 true-positives but 3 false-positives). These data confirm our belief that bilateral reductions in either metabolism or perfusion will provide a more accurate test. When unilateral reductions are used the specificity and false-positive rate will increase. In our study we chose to use visual criteria to grade the images rather than semiquantitative techniques because visual analysis is more commonly used in a clinical setting. Such differences in approach make it difficult to directly compare sensitivity, specificity, and diagnostic accuracy. Nevertheless the results appear to be similar for the SPECT rCBF and FDG PET approaches.

We do not agree with the statement that early diagnosis and differentiation of AD by clinical criteria is easy. Numerous studies from the literature give varying rates of diagnostic accuracy for clinical evaluation. In our own series of diagnostically challenging patients, the sensitivity, specificity, and diagnostic accuracy for the clinical diagnosis of AD was lower than for image-based diagnosis. It appears that at Dr. Bonte's institution the clinical and image-based evaluation of patients with dementia are now more consistent with the approach used in our study. In particular, SPECT rCBF imaging is used in those patients with confusing symptoms and test results. This approach is consistent with the evolving general practice of the medical community as well as at many academically oriented memory disorder or dementia clinics. However, functional imaging assessments may become more important in the early evaluation of patients with mild memory loss or difficult-to-characterize early dementia, or diagnostically challenging patients where a more accurate diagnosis is needed to confirm the suspected diagnosis. This early, accurate diagnosis is becoming much more important because new drug therapies for AD are now becoming available.

Our results and those of Bonte et al. appear to be very similar as to sensitivity, specificity, and diagnostic accuracy, and reflect the potential power of using a functional imaging technique in evaluating patients with dementia.

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