diopharmaceuticals for therapy (2). This final rule is unusual in that an expiration date was assigned to this regulation. The effective time period for this rule was set from August 23, 1992 to August 23, 1993, which is the same period of time as that for the Interim Final Rule on 10 CFR Parts 30 and 35. The inclusion of an effective time period for this final rule was necessary to allow the NRC to reconsider some of the issues raised by the American College of Nuclear Physicians (ACNP) and the Society of Nuclear Medicine (SNM) in their petition for rulemaking on 10 CFR Parts 30, 33, and 35 filed with the NRC on June 5, 1989 (3).

Although the NRC is eliminating the recordkeeping requirements under this final rule, they have clearly indicated in their responses to public comments that at this time they have no intention of terminating thc remainder of the Interim Final Rule (2). Thus, this final rule removes only the recordkeeping requirements related to the specific nature of the departure, i.e., a precise description of the departure, a brief statement of the reasons for the departure and the number of departures from the Food and Drug Administration (FDA) approved package inserts. The other parts of the Interim Final Rule should still remain valid. The issue of terminating the remainder of the Interim Final Rule will be addressed at a later time when the NRC has completed its consideration of the ACNP/SNM petition.

However, another difference seems to exist apart from the elimination of recordkeeping requirements between the Final Rule and the Interim Final Rule. Under the new final rule, departures from the manufacturer's instructions can be made by following the direction of an authorized user physician. The removal of the previous restrictions under the Interim Final Rule that deviations from the package insert can only be made if ". . . the departures would obtain medical results not otherwise attainable or would reduce medial risks to particular patients because of their medical condition . . ." (2) would seem to suggest that an authorized user physician may prescribe a departure from the manufacturer's instructions in the preparation of reagent kits for economic reasons. Examples of this type of departure include the addition of higher radioactivity to the reagent cold kit, allowing more unit doses to be dispensed from the same kit, and the fractionation of expensive radiopharmaceutical kits such as Ceretec™ (Amersham Corporation, Arlington Heights, IL), TechneScan MAG3™ (Mallinckrodt Medical, Inc., St. Louis, MO), and CARDIOLITE® (The Du Pont Merck Pharmaceutical Co., N. Billerica, MA) for cost reduction.

One of the major reasons that the NRC has decided to eliminate the requirements for recordkeeping related to the deviation is that both the NRC and the FDA have concluded that the major trends in departures from the package inserts have been identified based upon the documentation collected by the NRC, and they have agreed that there is no need to collect additional data. It is not clear whether the NRC had included the information with regard to the departures for economic purposes prior to their decision for amending the regulations. Even if the NRC and the FDA had not had a chance to review the documentation of deviations from manufacturer's instructions for reasons of cost saving, I believe that such departure should still be allowed under the new final rule as long as the procedures for deviation have been developed and evaluated in a scientific manner, and preferably that the procedures have been published in a peer-review professional journal. With well-established data to support the departure for cost effectiveness and the required direction for such deviation from an authorized user physician, the protection of the public health and safety can then be guaranteed, and therefore such a practice will not violate the NRC's legislative mandate.

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Correlation of Radiation Absorbed Doses to Nodal Metastases

TO THE EDITOR: In a recent study of thyroid cancer patients, Maxon et al. predicted radiation absorbed doses to nodal metastases from ^{131}I therapy and correlated them with the results of the therapy (1). They used 74 MBq (2 mCi) of ^{131}I plus conjugate views to calculate absorbed dose in a preliminary study and predicted the therapy absorbed dose by scaling with the ratio of administered activities (therapy over preliminary). In the preliminary study, patients were imaged at 24, 48 and 72 hr post-administration, instantaneous uptake was assumed and the lesion activity was plotted on semilog paper, then fit with a straight line. In 23 patients where nodal metastases were associated either with residual thyroid disease or with other metastic foci, a total of 36 lesions were analyzed quantitatively. The protocol predicted they would absorb a dose greater than or equal to 8,500 rads. Of the nodes receiving this dose, 86.1% (31/36) responded (as subsequently judged by physical examination and visual interpretation of images).

In our much smaller series, we used a pair of orthogonal views and imaged our patients after the therapy administration of radioiodine (2,3). When we had only one good view due to overlap of lesions in the other, we averaged two estimates of the volume (assuming two different ellipsoids of rotation in the good view) and found that an absorbed dose as low as 5,300 rads was sufficient to produce a response. When we had two unambiguous views, no averaging was necessary and a more accurate volume estimate was obtained. We determined that absorbed doses more than or equal to 2,400 rads (in one patient) or 3,460 rads (in another) were correlated with response. These three values are only 66% or less of the target value (8,000 rads) proposed by Maxon et al. Also, our intratherapy measurements of uptake versus time produced data sets that did not all fit a straight line. For five metastases, the peak uptake was at the first time point measured (average time 28 hr), but in four others, it was later (between 48 and 77.5 hr). Our measured effective half-life for washout averaged 1.59 days.

In view of our data, we have several questions regarding the results of the Maxon group. How well did a straight line fit the

data sets? What was the average effective half-life? For those patients who showed evidence of slow uptake, would the effective half-life and calculated absorbed dose be much lower if only the 48- and 72-hr points were joined by a straight line and an adjustment was made for the amount the 24-hr data point was below the extrapolated line? Would measurements during therapy produce values only 66% or less of their current values using their technique?

Our results indicate that absorbed doses lower than those calculated by Maxon et al. correlate with response. Refinements in their current protocol for predicting absorbed dose or measurements during therapy might eliminate the discrepancy. On the other hand, one could argue that a systematic error in our volume estimates caused the difference. It is also possible their current protocol produces a value for absorbed dose which works well enough as an index for handling thyroid cancer patients, or changes in their protocol might indeed lower any upward bias but, unfortunately, increase the variance of the calculated absorbed dose and thus be of questionable value. Our protocol was consistent in using the same pixels to estimate volume and uptake; this fact should have prevented propagation of error in the calculated dose. Overall, further research appears to be needed.

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REPLY: The paper (*1*) to which Drs. Koral and Adler refer is a clinical report that prospectively evaluated outcome when patients with thyroid cancer were treated on the basis of radiation absorbed doses calculated from diagnostic radioiodine studies using methods that we have described previously (*2,3*). The point was to validate the clinical utility of treatment thresholds derived from our initial studies (*4*) in a second, separate group of patients. The article is not about methodologies of quantitative dosimetry but rather deals with the clinical utility of quantitative dosimetry, using our methods, as a basis for therapy decisions.

Koral and Adler refer to one subgroup of our study population that consisted of 23 patients who had a total of 78 nodal metastases: 16 of 23 had nodal metastases as well as residual thyroid tissue and/or other metastases and 7 of the 23 had nodal metastases only. When all 23 patients were considered as a group, 74% of the patients and 81% of their nodal metastases responded to initial radioiodine therapy with complete resolution of the nodal metastases as judged by physical examination and visual interpretation of subsequent images. When we looked at the small subgroup of seven patients who had only nodal metastases then, at an average radiation dose of 14,000 rad, 86% of patients were treated successfully. This study was designed to evaluate the efficacy of using thresholds of 30,000 rad to ablate thyroid remnants and of 8500 rad for nodal metastases, and therefore none of the patients in this study were treated with lower doses.

In 1983 (*4*) we had demonstrated that, when doses of 8000 rad or more could be delivered to metastatic foci, then significantly more lesions responded to treatment than at lower doses between 3500 and 8000 rad (98% versus 63%, $p < 0.001$). None of the metastases in our original series responded to doses of less than 3500 rad. Kimmig and Hermann (*5*) also reported that three of four patients with metastatic foci receiving greater than 10,000 rad responded to treatment, whereas 0/7 who received less than 4000 rad to their metastases did so. Flower and colleagues (*6*) subsequently noted that only two of eight patients with nodal metastases appeared to respond to radiation doses less than 3000–4000 rad. Thus, while it is clear that there are occasional patients who will respond to lower radiation doses, the percentages that do so are quite small and are unacceptable clinically.

The comments offered by Koral and Adler are concerned mainly with techniques of dosimetry and are largely based on their earlier report of immediate post-^{131}I therapy studies (*7*), using a different methodology, in nine nodal metastases in four patients who responded to ^{131}I therapy. In that paper, one of three lymph node metastases quantitated in one patient showed a radiation dose that was "≥2400 rad" (upper limit of calculation not specified), whereas all of the other eight nodal metastases in the four patients received essentially 3500 rad or more, and five of the eight received more than 8000 rad. Thus, their findings are not inconsistent with our earlier observations (*4*).

With respect to some of their other questions, a single exponential curve fit the data in our patients quite well, and only one of our patients with nodal metastases demonstrated a delayed peak uptake at 48 hr. The range of effective half-lives of ^{131}I in the patients in question was 26-160 hr, underscoring the need for individualized quantitative dosimetry in each patient. We did not perform quantitative calculations after the actual therapeutic administrations since that would have increased patient morbidity by prolonging the period of time that the patients were required to maintain both a hypothyroid state and a low iodine, protein- and calorie-deficient diet.

Clearly, there are uncertainties in any dosimetric method employed, and I wish to iterate that our results are based on the conjugate view techniques developed here at the University of Cincinnati. In that regard, I am grateful for an opportunity to correct a misstatement in our most recent paper (*1*) that occurred on the last line of the last paragraph in the section on diagnostic ^{131}I scans on page 1133. I inadvertently included a description from another paper that I was writing at the same time on quantitative blood dosimetry and stated that "The effective half-time of ^{131}I in lesions was based on an exponential fit of those same uptake data, assuming only physical decay beyond 72 hr." In our quantitative dosimetric approach to the ablation of thyroid remnants and to the treatment of metastases, the effective half-time is based on an exponential fit of the uptake data only, and we do *not* assume physical decay beyond 72 hr. The methods remain those described by us earlier.

In summary, the quantitative dosimetric approach that we have developed does permit rational clinical decisions with pre-