that other investigators have reported flow cytometry data similar to theirs (*2*), and we have made similar observations in our unpublished data on the distribution of BrdU antigen in V79 cells.

As pointed out by Kvinnsland et al. in their letter to the editor, we measured the distribution of radioactivity at the cellular level using autoradiographic techniques (*3*), whereas they infer the distribution from fluorescence intensity measurements obtained with a flow cytometer. We use both techniques in our laboratory and each has its strengths and limitations. The autoradiographic approach is labor-intensive; however, it does actually measure the distribution as opposed to inferring it. Indeed, it is known that the distribution of radioactivity can be significantly different than the distribution of the antibody (*4*). One criticism of the authors with regard to the autoradiographic approach was that "the distribution has to be measured part by part by varying the concentrations of radiochemicals and exposure times." Whereas exposure times were varied to obtain track data that cover the entire distribution of cellular activity, concentrations were changed only to examine whether extracellular concentration of radioactivity influenced the shape of the distribution (Fig. 5 (*3*)). This should be done regardless of the measurement technique. Nevertheless, the authors of the letter raised an excellent question with regard to the potential influence of Poisson statistics on our autoradiographic track distributions and their subsequent analysis. Indeed, if each cell in the population had the same activity, then one would anticipate a Poisson distribution of measured tracks that would change with increasing expectation value (i.e., longer autoradiograph exposure times). With this in mind, the authors point out that our measured distribution may be a convolution of a Poisson distribution and an underlying distribution associated with the radioactivity. We were remiss in not definitively addressing the impact that this may have on our results. To investigate the impact of Poisson statistics on determining the distribution of radioactivity in the cell population from our autoradiographic data, it is necessary to return to the raw data in Figure 3 of Neti and Howell (*3*). Figures 3A, 3B, and 3C contain track distributions obtained from cell populations that were exposed to 0.52, 3.8, and 67 kBq/mL, respectively (*3*). The track distributions were acquired from autoradiographs that were developed at different times. Each set of track distribution data includes the number of cells scored with 0–9 tracks per cell as well as the number of cells with an unscoreable number of tracks (>9 tracks). We have examined the effect of Poisson statistics on our analyses of these data both before and after our convolution of the datasets. The data were analyzed with Poisson, log normal, and combined Poisson + log normal distribution functions. The Poisson distribution function is given by $P(n) = (c^n/n!)e^{-c}$, where n is the number of tracks per cell, c is the expected value $<n>$, and $P(n)$ is the probability of n discrete tracks per cell. The log normal distribution functions are given in (*3*). According to Fors et al. (*5*), the Poisson + log normal compound probability of obtaining a realization n given the mean c and all its possible Poisson realizations k is given by:

$$P(n|c) = \sum_{k=1}^{\infty} \frac{1}{\sqrt{2\pi}\,\sigma n} e^{-\frac{\left(\ln\frac{n}{k}-\frac{\sigma^2}{2}\right)^2}{2\sigma^2}} e^{-c}\frac{c^k}{k!},$$

where σ is the shape parameter. The capacity of these distributions to describe the various experimental data (t = 0.25, 0.67, 1, 4, 7, 26, and 52 d) were tested by reduced χ^2 ($\hat{\chi}^2$) analyses and compared.

As pointed out by the authors, the Poisson distribution shifts as the mean is increased. However, among the 3 distributions tested, the Poisson distribution gives the highest $\hat{\chi}^2$ value for every dataset (poorest fit to the data). The lowest $\hat{\chi}^2$ values are obtained with the log normal (t = 0.25, 0.67, 4, 7, 52 d) or Poisson + log normal distribution functions (t = 1, 7 d). A detailed analysis suggests that there is a significant Poisson component in some of the measured track distributions; however, the underlying distribution remains log normal. Notably, the shape parameters (σ) obtained by minimizing $\hat{\chi}^2$ are generally within uncertainties with respect to those that were obtained by a least-squares fit of the convolved data to a log normal function (*3*). It is our intention to publish the details of these analyses elsewhere.

The statistical analyses briefly described here support our conclusion that the distribution of radioactivity in the cell population is well represented by a log normal distribution. As mentioned earlier (*3*), it is possible that other distribution functions may better explain the experimental data and no attempt was made to ascertain this. We trust that because of the ubiquitous presence of log normal distributions across many fields (*6*), many investigators in radiation biology may find this distribution useful to fold into their dose–response models. Its implementation is facilitated by several factors. First, and foremost, it is an analytic function that is described by only 2 parameters (σ, μ). Second, the log normal probability density function is provided in standard subroutine libraries (e.g., National Algorithm Group). In closing, we thank Kvinnsland et al. and the editor for providing us with this opportunity to provide further support for the log normal distribution of radioactivity among a cell population.

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Stunning Effect

TO THE EDITOR: In the study by Sisson et al. (*1*), the authors have attributed the "so-called stunning effect" to the early effects of the treatment dose on ^{131}I accumulation. As noted in the accompanying invited perspective (*2*), this phenomenon has been described previously (*3,4*), but it does not preclude the existence

of the stunning effect otherwise attributed to a pretreatment diagnostic dose of ^{131}I. We would like to comment on the following points raised in the article.

As acknowledged by the authors (*1*), it is the absorbed dose—and less so, the administered dose—that will determine the effect of the ^{131}I radiation on the tissues (*5,6*). Therefore, it is not surprising that this study found a lack of precise correlation between the administered ^{131}I diagnostic dose (ranging from 18.5 to 74 MBq) and the measured treatment/diagnostic dose ratios. (However, Table 1 (*1*) does show the lowest ratio for the highest 37-MBq diagnostic dose group, even if this was not statistically significant.)

Second, it is technically challenging to accurately measure uptake of the posttreatment dose. The authors acknowledged their inability to do so at 24 h with patients given 5.5 GBq ^{131}I treatments. We would further ask whether the linearity of such other measurements in the posttreatment time interval was validated, as this was not mentioned in the article.

Third, the authors stated the following in the Discussion under Literature Comparisons: "In only one publication was ablation observed less frequently in patients who received treatment preceded by diagnostic imaging than in patients who were treated without diagnostic imaging. . ." (*1*). In fact, there have been multiple other such reports. Lees et al. (*7*) reported that preablation diagnostic whole-body scanning performed in 36 patients with 185 MBq of ^{131}I was associated with a 47% first therapy success rate, compared with 86% in the same number of patients who had been scanned with 740 MBq of ^{123}I. A significantly greater number of total treatments and more total radioiodine were required for complete ablation among the former group versus the latter. Similarly, Chmielowiec et al. (*8*) reported a significantly lower total cumulative ^{131}I dose and fewer treatments required to achieve complete ablation after ^{131}I treatment among 105 patients who had been diagnostically scanned with a lower ^{131}I dose before treatment, versus that among 126 patients who had been first scanned with a higher ^{131}I dose (average total treatment dose = 189.7 GBq vs. 275.8 GBq, and average number of treatments = 1.51 vs. 1.83, respectively; $P < 0.01$ for both). In addition, Park et al. (*9*) reported a 72% (34/47) ^{131}I treatment efficacy among patients diagnostically scanned with 11 MBq of ^{123}I versus a 56% (24/43) treatment efficacy of ^{131}I for patients first scanned with 111–370 MBq of ^{131}I ($P = 0.125$). Although this difference did not achieve statistical significance, a clear trend of decreased treatment efficacy was nonetheless suggested when pretreatment ^{131}I diagnostic scans were used. In conjunction with the study by Muratet et al. (*10*) cited by the authors, this represents a compelling consensus of data from a total of 658 patients in direct support of the deleterious impact of ^{131}I diagnostic doses on the subsequent ^{131}I treatment efficacy for ablation.

Finally, Hilditch et al. (*4*) also described a phenomenon similar to that of Sisson et al. (*1*) in which the early treatment effects of the ^{131}I treatment dose may have contributed to the measurement of a reduced percent uptake compared with that of the prior diagnostic dose. However, the therapy/diagnostic uptake ratios were less reduced for patients who had diagnostic scans with 200 MBq of ^{123}I versus those scanned with 120 MBq of ^{131}I before ^{131}I treatment (median values, 58.5% vs. 32.8%, respectively; $P < 0.001$). Importantly, this decrement was more significant when compounded with the stunning pretreatment effect of the ^{131}I diagnostic dose. Conversely, this effect was quantitatively lessened by the use of ^{123}I instead of ^{131}I for the pretreatment diagnostic scan.

Notwithstanding potential concerns about the accuracy of measuring posttreatment ^{131}I uptake, it is conceivable that the early treatment effect could contribute to a lower measured uptake from a number of possible mechanisms. Regardless, however, we maintain that this effect would be independent of the potential deleterious effects of a prior diagnostic ^{131}I dose, a potentially significant avoidable liability that should not be discounted. We continue to advocate the use of ^{123}I when available—or, alternatively the lowest possible ^{131}I dose—for the purposes of diagnostic scanning to minimize the potential risks of compromising subsequent therapeutic efficacy caused by stunning (*11*).

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REPLY: The correspondents argue that ^{131}I in diagnostic doses has the potential to cause "stunning" of the uptake of the subsequent ^{131}I treatment dose that is given to patients with well-differentiated thyroid carcinomas. We agree that the energy deposited by ^{131}I can injure the function of residual thyroid tissues, benign and malignant. However, the questions are (i) what administered dose of diagnostic ^{131}I is unlikely to produce significant impairment of the subsequent treatment? and (ii) is there a more efficacious method of preliminary evaluation of patients who are candidates for the therapy?

Determination of the absorbed dose of radiation from a given administered dose of ^{131}I is not possible with our current methods. However, from our literature review (*1*), it seems likely that 1 mCi (37 MBq) will produce modest, if any, impairment of function in the target tissues. In any case, the largest differences between