On the basis of this experience, we would like to raise the following points with regard to the article by Sisson et al. (*1*):

1. We agree that [^{125}I]MIBG has a place in the treatment of neuroblastoma micrometastases and bone marrow infiltration, particularly as the results of [^{131}I]MIBG treatment under these circumstances are poor. We have used lower activities than Sisson et al., but have observed no toxicity whatsoever. The use of [^{125}I]MIBG for therapy, especially at higher doses, does pose a problem of radioactive waste, which requires responsible attention from nuclear medicine specialists.
2. In contrast to Sisson et al., the images accompanying this letter demonstrate that post-therapeutic scintigraphy using [^{125}I]MIBG is feasible and that the images obtained are also of acceptable quality.
3. In discussing the rationale for using [^{125}I]MIBG to treat neuroblastoma, Sisson et al. have overlooked the fundamental observations by Smets et al. (*5*), which indicate the most promising basis for this radiopharmaceutical, particularly in neuroblastoma, in that extragranular storage contributes significantly to total MIBG retention. The cytoplasmic and homogeneous distribution of [^{125}I]MIBG may result in a lethal radiation dose to the nucleus.
4. Finally, we do wish to stress that by pursuing [^{131}I]MIBG therapy at our institute (230 therapeutic applications in 75 patients to date), we have observed complete remissions and long-term responses, despite the fact that most of these patients had progressive Stage IV neuroblastoma and were only treated with [^{131}I]MIBG after all other treatment options had failed. We are convinced of the efficacy and safety of [^{131}I]MIBG in children, provided that the bone marrow is not involved by tumor. The observed response in advanced neuroblastoma, the non-invasive nature of the procedure, and the high metabolic activity of untreated tumors have permitted us to use preoperative [^{131}I]MIBG successfully instead of combination chemotherapy for inoperable neuroblastoma (*6*). The advantages of this approach are that the child's general condition is usually good prior to surgery and that chemotherapy is reserved to treat minimal residual disease, when it is likely to be most effective. Iodine-125-MIBG therapy may also be indicated in these circumstances.

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REPLY: We thank Dr. Hoefnagel and colleagues for the references to their work. We, too, reported part of our work in abstract form (Eur Assoc Nucl Med Congress, 1989; *J Nucl Med* 1990;31:804) but elected not to quote abstracts in our recent paper (*1*). Moreover, this paper described the initial toxic effects of [^{125}I]MIBG as a single agent in a dose-escalation program which differs from the apparent purpose of Hoefnagel et al.

Images of neuroblastoma can be made with [^{125}I]MIBG as shown by Hoefnagel et al. But quantification of MIBG within regions of the body, including the tumors under treatment, has been difficult using [^{131}I]MIBG, and this goal becomes a formidable challenge when MIBG is labeled only with ^{125}I.

We agree with the Dutch investigators that [^{131}I]MIBG has effects on neuroblastoma. However, the optimum use of [^{131}I]MIBG, and of [^{125}I]MIBG, will remain uncertain until there is a controlled trial of therapy with these agents.

Our hypothesis for the treatment of neuroblastoma with [^{125}I]MIBG is: at acceptable levels of toxicity, [^{125}I]MIBG will be more effective in destroying micrometastases than [^{131}I]MIBG. We have shown that per mCi or MBq administered [^{125}I]MIBG is less toxic (*1*). Nevertheless, [^{125}I]MIBG will be toxic as doses are increased, and it is likely that optimum treatment of neuroblastoma will require the highest doses possible. Therefore, a dose-escalation study of [^{125}I]MIBG is a prerequisite to testing our hypothesis. Such a study is also a necessary foundation for optimum therapy with [^{125}I]MIBG under any circumstance.

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Effective Background Correction on Separate Technetium-99M-DTPA Renal Clearance

TO THE EDITOR: In a recent paper on the measurement of individual kidney glomerular filtration rate (IKGFR) from the technetium-99m-DTPA (^{99m}Tc-DTPA) renogram, Piepsz

et al. (*1*) compared three analytical approaches (algorithms) and three choices of extra-renal regions of interests (ROIs) for background correction.

The fundamental assumption required of any background ROI, irrespective of the algorithm used, is that the GFR equivalent (GFRe) in the extravascular compartment of the ROI (i.e., the effective clearance rate of ^{99m}Tc-DTPA from intravascular to extravascular compartments within the region) is the same as that in the non-renal tissue within the renal ROI. With the exception of the double correction method, this assumption also applies to the GFRe (which is negative) of the intravascular compartment of the ROI (i.e., the magnitude of the error imparted to the calculated IKGFR by the falling intravascular signal).

We quantified these GFR equivalents in a peri-renal ROI like that described by Piepsz et al., showing them to be of the order of 30 and −50 ml/min/1.73m^2, respectively (*2*). The size of the intravascular GFRe explains why the mean IKGFR, of the right kidney in Piepsz's paper was actually negative (and for the left kidney almost zero) when using the surface method algorithm combined with a background ROI below the kidney. Thus, the positive GFRe for the extravascular compartment within the renal ROI was appropriately subtracted (if not oversubtracted) while the negative intravascular GFR equivalent within the renal ROI was greatly undersubtracted. We also showed that the proportion of GFR equivalents of intravascular and extravascular background compartments was almost identical between a renal ROI and a peri-renal background ROI, and that their absolute values were also quite close between the two ROIs, validating and supporting the use of a peri-renal background ROI (*3*).

In order to use these algorithms for measurement of IKGFR, it is necessary to continuously record plasma activity. The usual way to do this is to place a ROI over the cardiac blood pool. This introduces an additional background problem since the cardiac blood-pool signal is "contaminated" by ^{99m}Tc-DTPA, which progressively accumulates in the extravascular space of the chest wall within the ROI. This introduces a potentially important error which Piepsz et al., as well as other workers (*4–6*), have not addressed.

Using a small dose of ^{99m}Tc-human serum albumin (HSA) given 5 min before the ^{99m}Tc-DTPA, we have quantified the proportion of the signal in the cardiac blood-pool ROI that results from extravascular ^{99m}Tc-DTPA in the chest wall in 12 patients undergoing routine renography for outflow tract obstruction (*7*). Equal-sized ROIs were placed symmetrically over the chest from the posterior projection, one over the cardiac blood pool and the other over the right lung, and the respective time-activity curves, $C_{DTPA}(t)$ and $L_{DTPA}(t)$, were generated. Since, in both ROIs, the extravascular signal, E(t) arises very predominantly from the chest wall, we can say that $[C_{DTPA}(t) - E(t)]/[L_{DTPA}(t) - E(t)]$ is equal to a constant, R, following the first few passes of DTPA. Provided that the HSA remains intravascular, then the ratio of the HSA signals in the respective chest ROI will also be equal to R.

$$\text{Therefore,} \quad E(t) = \frac{[R.\ L_{DTPA}(t)] - C_{DTPA}(t)}{R - 1}$$

from which we can derive $E(t)/C_{DTPA}(t)$.

The dose of ^{99m}Tc-HSA was about 40 MBq and that of ^{99m}Tc-DTPA about 300 MBq. The HSA signal was recorded for 5 min after which it was assumed to be constant over the brief period, 15 min, during which the DTPA data were acquired.

The extravascular signal in the ROI over the left ventricle was 11% (s.e. 2.1) of the total signal at 1.5 min after DTPA injection, 27% (2.6) at 5 min, 36% (2.4) at 10 min, and 35% (2.5) at 15 min. In other words, the plasma signal fell to less than twice the extravascular signal by 10 min. The error generated in the IKGFR by the use of an uncorrected cardiac blood-pool curve is greater the larger the cardiac blood-pool ROI. For an ROI restricted to the hottest area of the left ventricle (an area of about 36 pixels on a 64 × 64 matrix), it was 17% (3). This is less than one might expect and is reduced by a tendency for errors to cancel. Thus, the error leads to an underestimation of the unitless renal clearance (the C of Piepsz) but overestimates the gamma camera blood-pool signal, which is compared with the 20-min blood sample for the conversion of C to clearance with absolute units.

Therefore, it is necessary to choose the appropriate ROI for the kidney, its background, and the cardiac blood pool, as well as to use the appropriate algorithm for analysis of the renal curves. With regard to the cardiac blood pool, it is important to: (1) limit the size of its ROI to the smallest compatible with adequate counting statistics and (2) consider a means of subtracting extravascular background. Although theorectically attractive [because of the elimination of E(t)], the use of an ROI over the lung results in a subtracted curve with rather too few counts. An ROI below the kidneys, where the intravascular signal is relatively small, may be preferable but will probably require scaling down, as has been shown by Fleming for hippuran (*8*).

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