

Roland Muller-Suur
Karolinska Institute
Danderyd, Sweden

G. Schreij
P.W. de Leeuw
Academisch Ziekenhuis Maastricht
The Netherlands

REPLY: We thank Dr. Müller-Suur for his interest in our article. We reported the intra- and interobserver agreement between experienced nuclear medicine physicians who evaluated renograms. The agreement was found to be reasonably good, but the sensitivity and post-test probability of their renographic diagnosis in relation to the angiographic diagnosis was rather poor (1).

Numerous reports have documented a sensitivity and specificity ranging from 41% to 100% (2). However, almost all of these studies were performed retrospectively and all of them excluded patients with a "negative" renogram from undergoing renal angiography. Consequently, we have never been informed about the true false-negative rate of renography. Moreover, several investigators did not define the degree of stenosis that was considered to be significant. For these reasons, we think that most of these studies do show better results than ours, even though some also report a low sensitivity (2).

We also agree that renal angiography only determines the degree of stenosis and does not foretell whether a stenosis is hemodynamically responsible for the development of hypertension. A diagnosis of a hemodynamically important stenosis (causing hypertension), however, can only be made retrospectively, i.e., after correction of the stenosis. Since the renographic criteria of a hemodynamically important stenosis have not been formulated unequivocally and since no clinician will refrain from ordering a renal angiogram in a patient with a positive renogram, the concept of a hemodynamically important stenosis has no practical consequences for the screening of patients suspected of having renal artery stenosis. Furthermore, when an intervention fails to lower the blood pressure, this does not confirm renovascular hypertension, but does not exclude this diagnosis either.

All three readers who participated in our study are skilled nuclear medicine physicians with many years of academic practice experience, and they are familiar with the pitfalls of renogram interpretation. All the patients in the study had renograms performed in the morning after an overnight fast. Voiding of at least 1 cc/min during the investigations was also ensured. Antihypertensive drugs were discontinued at least 3 wk before the tests (which, incidentally, was not always done in other studies).

Our experiences with the plasma renin response to captopril in 49 patients have been published elsewhere (3). The baseline and captopril renograms of the first 28 patients in that series were used in our study. The receiver-operator characteristic curves of both baseline and postcaptopril peripheral renin levels indicated that renin levels did not discriminate between patients with essential hypertension and patients with renal artery stenosis.

In conclusion, we still feel that the use of (captopril) renography in patients with a strong clinical suspicion of renal artery stenosis is of limited screening value, based on many reports of studies that have not been performed prospectively or that excluded patients with a "negative" renogram from undergoing renal angiography. Therefore, we recommend further research in this area. This research should concentrate on new radiopharmaceutical tracers and on better criteria to define the hemodynamic significance of renal artery stenosis.

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Discordant Uptake of MIBI and HMPAO

TO THE EDITOR: We read with interest the case report of Shih et al. (1) on discordant uptake of ^{99m}Tc -MIBI and ^{99m}Tc -HMPAO uptake of recurrent occipital meningioma on brain SPECT images. We have recently performed a similar study on 20 primary, 15 metastatic and 4 unverified brain tumors, and on 12 patients with recurrent brain tumors. This report was accepted for oral presentation at the forthcoming EANM Congress in Copenhagen in September 1997 (2). Increased accumulation of MIBI was found in 7/7 meningiomas, 7/11 gliomas, 2/2 neurilemmomas, 2/4 unverified and 10/15 metastatic tumors (total 41 patients). In the patients with recurrent tumor, we found increased MIBI accumulation in 7/8 recurrent meningiomas and 3/4 recurrent gliomas. Technetium-99m-HMPAO studies were much more discordant (28 patients). Increased accumulation was found in 2/7 meningiomas and decreased activity was found in 4/7. In the glioma subgroup, increased accumulation was found in 3/11 gliomas and decreased activity was found in 2/11. For metastatic tumors, increased activity was found in 2/8 patients and was decreased in 6/8.

Augmentation of the MIBI image was achieved by delayed imaging after 4 hr (3/6 patients) or by repeating the study after intravenous injection of aminophylline (4/6 patients). These results indicate some usefulness of ^{99m}Tc -MIBI scanning when PET is unavailable, especially in meningiomas and recurrent tumors. As for HMPAO, we agree with Shih et al. (1) on the limited value of MIBI/HMPAO scanning in brain tumors—it may be, with the exception of metastatic tumors, where decreased uptake is frequent.

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Piotr Lass

Department of Nuclear Medicine
Medical University
Gdansk, Poland

Evaluating the Significance of Changes in Brain SPECT

TO THE EDITOR: The article by Ito et al. (1) presents a potentially valuable addition to the subject of SPECT evaluation of depression. The significance of their results is difficult to evaluate due to apparent conflicts in the description of their statistical methodology.

The article states that a voxel-by-voxel analysis was performed, and that for the bipolar and unipolar groups a Student's *t* value of 2.10 and 2.16, respectively, was used as their Bonferroni adjusted cutoff points for generating the results images presented.

Unfortunately, this statement does not appear to be supported by their data. Indeed for 18 and 13 degrees of freedom, respectively (based on the number of patients given for the three groups) and an uncorrected value of $p = 0.05$, the statistical table for critical *t* values (2) shows exactly the 2.10 and 2.16 values reported as thresholds. Even a minimal Bonferroni correction would have had to generate a much lower *p* value:

$$\frac{p}{\text{no. of uncorrelated areas}}, \quad \text{Eq. 1}$$

and thus a much higher critical t threshold. Consequently, it must be assumed that no Bonferroni correction was done and, thus, that the results have questionable significance. If a Bonferroni correction would have been performed for this voxel-by-voxel analysis (tens of thousands of voxels), the t thresholds would have become so high as to most likely negate any difference between the maps of control subjects and patient groups. Furthermore, the authors do not give any additional information about the number of voxels included in the analysis, the smoothing used or other means of diminishing the number of multiple comparisons. This further limits the possibility of objectively evaluating their results.

Given the potential value of studies like the one by Ito et al. (1) for the development of future brain SPECT paradigms, we believe that it is important for brain imaging studies to routinely provide a complete description, or reference, concerning the statistical methodology used for measuring significant change. This would enable a better evaluation of the results and, most importantly, their potential diagnostic impact.

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Dan G. Pavel

*University of Illinois Medical Center
Chicago, Illinois
Laboratory of Neurosciences
National Institute of Aging
Bethesda, Maryland*

J.D. Van Horn

*PET Unit
Clinical Brain Disorders Branch
National Institutes of Medical Health
Bethesda, Maryland*

Intracellular Fate of Radiometals

TO THE EDITOR: We wish to clarify an issue raised by two recent editorials in *The Journal of Nuclear Medicine* (1,2). Both editorials discussed renal accumulation of radiolabeled polypeptides and suggested that radiometals are retained by the kidney because they are bound by intracellular metal binding proteins. Both editorials then incorrectly cited studies with ^{111}In -DTPA-glycoproteins (3) as evidence of possible transchelation. While radiometal accumulation in the liver and kidneys have often been attributed to dissociation of the metal from its chelate, there is little evidence supporting transchelation to intracellular proteins. Instead there is ample evidence indicating that the radiometal accumulation reflects "trapping" of a radiolabeled metabolite within lysosomes.

Lysosomes are intracellular organelles that house a series of degradative enzymes (4). These enzymes rapidly degrade most polypeptides and the resulting amino acids are transported across the lysosomal membrane by a series of transport proteins (5). Polypeptides which cannot be degraded and certain amino acid derivatives which are not recognized by the transport proteins accumulate within lysosomes (6). This is empirical evidence that the other routes out of lysosomes are slow.

Lysosomal degradation of radiolabeled polypeptides yields a variety of radiolabeled metabolites which usually include a radiolabeled structure still linked to an amino acid (3,7-10). Thus, polypeptides labeled with radiometals using bifunctional chelates are degraded to metal-chelate-amino acid. The fact that with several chelates the metal-chelate-amino acid metabolites accumulate in lysosomes indicates that these metabolites are not rapidly released from lysosomes and that the metal chelate bond is stable within lysosomes (3,7,11). The cases where the metabolites are rapidly released suggests that these particular metabolites are recognized by transmembrane transporters and transferred across both the lysosomal and plasma membranes (11).

Thus, the available evidence indicates that cellular retention of many radiometals reflects trapping in lysosomes rather than transfer to intracellular metal binding proteins. While dissociation of certain radiometals in lysosomes could explain the accumulation of some radiometals in certain tissues (12), we hope that this additional information focuses attention on the important question of what happens to radiolabeled polypeptides once they are delivered to lysosomes.

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James R. Duncan

*Washington University Medical Center
St. Louis, MO*

Thomas M. Behr

*Friedrich Alexander
University of Erlangen-Nuremberg
Nuremberg, Germany*

Sally J. DeNardo

*University of California
Davis, California*