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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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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