hemocytometer. Any preparation that does not meet all of our quality assurance standards is discarded and replaced by a new preparation. The vial and syringe are well shaken during labeling and prior to tracer injection. Our technologists (all registry-certified) are very aware of the need to keep blood from entering the syringe containing the tracer, and most of our tracer injections are done through previously placed scalp vein needles. Finally, our image data are at variance with the possibility of poor tracer preparation, or inadvertent labeling of blood clots, or excess statistical noise from inadequate image data collection. Our images rarely show more than minimal pertechnetate activity in the stomach or thyroid; none of our studies show hot spots (QM) in the lungs—the principal scintigraphic manifestation of radiotracer trapped in blood clots; and contrary to what is expected of statistical noise, the QM findings were present only in individuals with shunts and absent in the images of patients without shunts.

Since the presence of imaging artifacts or improper radiopharmaceutical preparation do not appear to be plausible explanations for the discordant results in clinical studies done in Iowa City and Hannover, we refocused our attention on the image data. According to their communication, our German colleagues evaluate right-to-left shunts by using the images of the kidneys as a diagnostic and quantitation standard (instead of our practice of estimating extrapulmonary counts from images of the entire body), and they assume in patients with right-to-left shunts that the extrapulmonary activity would be four times the kidney activity. They obtain scintigrams of the brain in some or all cases, but apparently do not record scintigraphic images of the rest of the body. Could it be that the QM pattern we observed in our shunt patients rarely occurred on images of the kidneys? To evaluate this possibility, we retrieved the image data of the last 10 patients with proven right-to-left shunts and re-examined the images. Only 2 of the 10 studies showed a faint QM pattern on the kidney images (easily missed), even though all 10 showed unmistakable QM patterns in the soft tissues of the lower torso and extremities (see example in Fig. 1), and 9 showed a less noticeable QM pattern on images of the brain. In view of this, we can only speculate that Meins et al. may have missed seeing QM patterns in shunt patients, because they were not able to review images of the lower abdomen, pelvis and extremities.

One can theorize further on the implications of these observations. Patients with moderately large right-to-left shunts may deposit a sufficiently large number of MAA particles in the kidneys to avoid the nonuniform tissue distribution of particles that we believe to be the cause of the QM phenomenon. This explanation is consistent with the lack of any QM patterns in the lungs of our subjects. This argument also provides at least theoretical support to the hypothesis stated by Meins et al. that large shunts may obscure QM patterns in children due to their smaller volume of distribution for the shunted particles. Our own limited experience, however, indicates that the ratio (MAA particles)/(distribution volume) may not be sufficiently large in the peripheral tissues of even small children with large shunts, since we observed the QM pattern in three young children (ages 1 mo, 3 mo and 3 yr) with moderate-sized shunts (13%, 23% and 24%). Interestingly, none showed a QM pattern on the images of the kidneys, but two showed QM patterns on the brain images.

Whether our speculative explanation of the discordant findings at two reputable institutions is valid remains to be seen. As we stated in our original article, our observation is based on a relatively small number of patient studies. Since our "new scintigraphic sign" has the potential for considerable clinical value, it deserves evaluation and confirmation by other groups. We thank Meins et al. for their response to our article; and, once again, we invite other clinical centers, and especially our pediatric nuclear medicine colleagues, to test the value of our observation in larger sets of patients with right-to-left shunts.

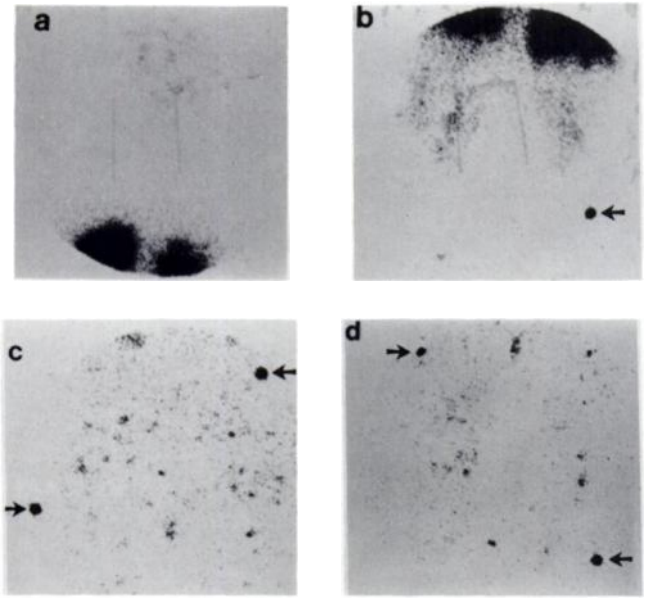

FIGURE 1. Scintigraphic images of ^{99m}Tc-MAA distribution in a 12-yr-old with an estimated 11% right-to-left shunt. The arrows indicate skin markers (cf. original article). A quantum mottle pattern is probably present in both brain (a) and kidneys (b), but is hard to identify with certainty, whereas it is very obvious on images of the pelvis (c) and thighs (d).

Peter T. Kirchner
Karim Rezai
Semih Dogan
The University of Iowa
Iowa City, Iowa

Treating Hyperthyroidism with Radioiodine

TO THE EDITOR: I was particularly interested in Dr. Shapiro's editorial comments (*1*) on the article of Bockisch et al. (*2*) in the October issue of *JNM* concerning the treatment of hyperthyroidism with radioiodine.

Bockisch insists on the differences in thyroid pathology between the United States and Europe, a fact that I stress whenever I have the opportunity. This means that results of clinical studies cannot be extrapolated without caution when crossing the Atlantic Ocean. This is of course due to the differences in alimentary iodine, as he mentioned.

It is nevertheless unfortunate that he did not further discuss the consequences of this fact regarding the treatment of hyperthyroidism with radioiodine. In our experience, the amount of stable thyroidal iodine pool (ITI) plays a crucial role and should be put in front of the "fudge factors" he lists in his Table 2.

Using the x-ray fluorescence method to measure ITI, we showed that autonomy can be explained in toxic nodules, at least in part by the fact that they are still able to store iodide in contrast

to toxic nodules within the frame of Graves' disease that cannot. Furthermore, hyperthyroid patients with an increased ITI are more resistant to treatment (*3*). We also showed that a high IU (>40%) does not exclude iodine excess, nor does a normal urinary iodide, and the PB*I at 24 hr correlates negatively with ITI so that this measurement can be used to predict the iodide stores of the gland (*4*).

Of course, we are aware that the possibilities of measuring ITI are very scarce. Nevertheless, as we estimate that more than 30% of our hyperthyroid population present with iodine excess (especially the elderly as they need more radiodine), it is important to recognize some indicators that can be overlooked. Aside from the classical features, such as knowledge of iodine intake, a low IU and an increase of urinary iodide, the following factors should alert the physician to the possibility of iodine excess (at least in areas with relatively low iodine intake): a nonautoimmune toxic nodular goiter with a low PB*I at 24 hr and a suspiciously high T4/T3 ratio. Radioiodine treatment should then be adapted accordingly.

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M.H. Jonckheer
Vrije Universiteit Brussel
Brussels, Belgium

REPLY: Your concurrence with the important differences between thyroid disease in Europe and the United States is of interest.

The points you make about the in intrathyroidal iodine pool are very well taken. Indeed I meant for this to be included as one of the many influences under the specified and unspecified "fudge factors" in Table 2.

X-ray fluorescent thyroid scanning to depict and quantify intrathyroidal iodide stores is an important and unique technique (providing data unavailable by RIU or urinary iodide measurements). My reason for not discussing the problems of variable intrathyroid iodide stores was primarily the space limitation for such editorials and the unfortunate fact that the technology of fluorescent thyroid scanning has not become widely disseminated and is not generally available in the U.S. (indeed no commercial devices are available). The alternative and much more readily performed study which is to determine the ^{131}I-PBI, as well as the ^{131}I-RIU, at 24 hr after tracer administration is an excellent suggestion and should be more widely practiced since it is within the ability of almost any laboratory with a wellcounter.

B. Shapiro
University of Michigan Medical Center
Ann Arbor, Michigan

Understanding Intracellular Metabolism: A Key to the Rational Design for Targeting Drugs and Radionuclides

TO THE EDITOR: I read with interest the article by Duncan and Welch on the intracellular metabolism of ^{111}In-DTPA-labeled receptor-targeted proteins (*1*). They demonstrate that in vitro these proteins are degraded in the lysosomes and that low molecular weight catabolites are formed containing the ^{111}In label. In follow-up studies, they have identified the metabolite as ^{111}In-DTPA-lysine. This metabolite remains in the lysosomes and is only slowly released from the cell. This may be one of the causes of the high renal and hepatic tracer accumulation as observed in scintigraphy of ^{111}In-labeled monoclonal antibodies.

This work shows an interesting relation with my studies on the targeting of drugs to the kidney and the liver using low molecular weight proteins and neoglycoproteins as carriers (*2–5*). In this concept of drug targeting, the lysosomal apparatus regenerates the active (parent) drug. In these studies, drugs were conjugated to proteins using a method similar to that applied by Duncan and Welch for ^{111}In-DTPA conjugation, i.e., an amide bond between the drug and the amino groups of proteins. My co-workers and I have demonstrated that lysosomal digestion of these conjugates results in drug-lysine compounds rather than the parent drugs (*2*). For instance, the anti-inflammatory agent naproxen conjugated to the low molecular weight protein lysozyme or to (neoglyco)albumins renders naproxen-lysine in lysosomal lysates. This is similar to the finding by Duncan and Welch that ^{111}In-DTPA-lysine is the major radioactive metabolite of lysosomal targeted proteins.

In contrast, as observed for ^{111}In-DTPA-lysine in vitro, naproxen-lysine is capable of leaving cells. This has been demonstrated for the lysosomal processing of naproxen-lysozyme and various naproxen-(neoglyco)albumin conjugates in vitro as well as in vivo (*3,4*). This suggests that derivatization of the ε-amino groups of lysines *per se* does not prevent lysosomal-efflux of lysine-derivatives; rather, other molecular characteristics such as size, charge and lipophilicity of the drug or nuclide-chelator complex may determine lysosomal efflux properties. Therefore, it might be interesting to learn whether ^{111}In-DTPA-COOH can be lysosomally regenerated in its parent form and whether it is capable of leaving lysosomes.

In targeting drugs with proteins, a spacer between the drug and the protein is essential to regenerate the coupled drugs in their parent form in the lysosomes. In this respect it will be interesting to investigate whether the lysosomal efflux can be modulated by using different coupling modalities to the protein. In principle, two different approaches may be of interest. One is the use of enzymatically degradable spacers, like L-lactic acid derivatives and the other is the use of acid-sensitive linkages. In the former case, DTPA can be indirectly attached to the protein via an ester bond. Ester bonds may be lysosomally cleaved by various carboxyesterases as demonstrated for naproxen coupled to proteins via alpha-hydroxy-acid spacers (*2,5*).

Due to the narrow specificity of lysosomal enzymes, the connecting bonds between drugs and amino acids often remain intact in lysosomes (*2*); therefore, an even more viable approach may be using acid-sensitive spacers between the chelator and the protein-backbone. One possibility may be the use of a *cis*-aconityl-like amide bond (*2*). In this concept the amide bond that is stable in the bloodstream is selectively cleaved in lysosomes due to the acid environment (pH = 4–5). The advantage of this approach above