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.

REFERENCES

1. Shapiro B. Optimization of radioiodine therapy of thyrotoxicosis: what have we learned after 50 years? (Editorial). *J Nucl Med* 1993;34:1638–1641.
2. Bockisch A, Jamitzky T, Derwanz R, Biersack HJ. Optimized dose planning of radioiodine therapy of benign thyroid diseases. *J Nucl Med* 1993; 34:1632–1638.
3. Jonckheer MH, Velkeniers B, Vanhaelst L, Van Blerk M. Further characterization of iodide-induced hyperthyroidism based on the direct measurement of intrathyroidal stores. *Nucl Med Comm* 1992;13:114–118.
4. Jonckheer MH, Flamen P, Velkeniers B, Vanhaelst L, Kaufman L. Radioiodine turnover studies as a means to predict stable intrathyroidal iodine stores and comments upon its use in the diagnosis and treatment of hyperthyroidism. *Thyroid* 1993;3:11–16.

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