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 (es-
specially 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 ac-
cordingly.

REFERENCES

1. Shapiro B. Optimization of radioiodine therapy of thyrotoxicosis: what have
2. Bockisch A, Jamitzky T, Derwanz R, Biessack HJ. Optimized dose planning
34:1632–1638.
3. Jonckheer MH, Velkeniers B, Vanhaelet L, Van Blerk M. Further character-
ization of iodide-induced hyperthyroidism based on the direct measure-
iodine turnover studies as a means to predict stable intrathyroidal iodine
stores and comments upon its use in the diagnosis and treatment of hyper-
thyroidism. Thyroid 1993;3:11–16.

M.H. Jonckheer
Vrije Universiteit Brussel
Brussels, Belgium

REPLY: Your concurrence with the important differences be-
tween 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 in-
trathyroidal iodide stores is an important and unique technique
(providing data unavailable by RIU or urinary iodide measure-
ments). My reason for not discussing the problems of variable
intrathyroidal 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
device are available). The alternative and much more readily
performed study which is to determine the 131I-PBI, as well as the
131I-RIU, at 24 hr after tracer administration is an excellent sugges-
tion 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 111In-DTPA-labeled re-
ceptor-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 111In label. In follow-
up studies, they have identified the metabolite as 111In-
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 111In-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 111In-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)albu-
mins renders naproxen-lysine in lysosomal lysates. This is similar
to the finding by Duncan and Welch that 111In-DTPA-lysine is
the major radioactive metabolite of lysosomal targeted proteins.

In contrast, as observed for 111In-DTPA-lysine in vitro, naproxen-
lysine is capable of leaving cells. This has been demon-
strated 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 e-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 com-
plex may determine lysosomal efflux properties. Therefore, it
might be interesting to learn whether 111In-DTPA-COOH can be
lysosomally regenerated in its parent form and whether it is ca-
pable 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 enzy-
matically 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 carboxy-
sterases as demonstrated for naproxen coupled to proteins via
alpha-hydroxy-acid spacers (2,5).

Due to the narrow specificity of lysosomal enzymes, the con-
necting 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