the enzymatic approach is that in principle no enzymes are required to cleave these kinds of bonds.

I share the authors' view that intracellular metabolism can very well be studied in in vitro model systems; however, it should be noted that in vitro procedures may suffer from limitations like decreased enzyme activity of cell-homogenates and lysosomal lysates. These can be caused by isolation artefacts, like loss of co-factors during the work-up of these preparations. Therefore, a combination of in vitro and in vivo studies are needed to obtain optimal results on the intracellular metabolism of receptor-targeted proteins. Finally, the identification of metabolites like $^{111}$In-DTPA-lysine contributes to the understanding why high background radioactivity of labeled monoclonal antibodies is observed in the liver and kidneys. Improved knowledge on this point aids in the rational design of improved drug/nuclide targeting preparations.

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**REPLY:** We appreciate Dr. Franssen's interest and insightful comments. We agree entirely with the central theme of his letter: an understanding of intracellular metabolism will be key in the rational design of targeted drugs and diagnostic agents. We also agree with his contention that derivatization of the $\epsilon$-amino group of lysine does not prevent lysosomal efflux of lysine derivatives per se. Rather, we suggested that $^{111}$In-DTPA-amino acids would remain within the lysosome since their positive and negative charges would limit diffusion across the membrane (*1*). We also believe that size, charge and lipophilicity of the drug or nuclide-chelator will determine lysosomal efflux properties. When identifying in vivo metabolites, we found the predominant metabolite was $^{111}$In-DTPA-$\epsilon$-lysine and only small amounts of $^{111}$In-DTPA were produced (*2*). We were pleased to find Dr. Franssen's work, as well as other reports that suggest that lysosomes infrequently hydrolyze the amide bonds between lysine and "foreign" substances such as drugs and chelates.

We also hope to modulate the rates of lysosomal efflux through appropriate choices of chelates and their linkages to protein backbones. We plan to test these using reconstituted systems, cell culture models and in vivo experiments.

In summary, we hope all our correspondence with this journal will be in the same tone of complete agreement.

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## TBI Is Not MIBI

**TO THE EDITOR:** I read with great interest the case report by Desai and Yuille describing $^{99m}$Tc-MIBI uptake in a recurrent carcinoid tumor (*1*). Three $^{99m}$Tc-labeled isonitriles have been evaluated in detail in humans: TBI (tertiarybutyl isonitrile), CPI (carbomethoxyl isopropyl isonitrile) and MIBI (methoxy isobutyl isonitrile) (*2–4*). High uptake in the lung and liver limited the clinical use of $^{99m}$Tc-TBI (*2,5–7*). However, $^{99m}$Tc-MIBI, an ether-substituted analog of $^{99m}$Tc-TBI, has gained wide clinical acceptance.

Desai and Yuille stated that Ramanathan et al. (*8*) had used $^{99m}$Tc-MIBI for visualization of suppressed thyroid tissue, confusing TBI with MIBI. In fact, Ramanathan et al. have used $^{99m}$Tc-TBI for this purpose. Although both $^{99m}$Tc-MIBI and $^{99m}$Tc-TBI are essentially isonitriles, they have different chemical structures, biological behavior and in vivo distribution (*2,5–11*).

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## Modeling of Tumor Uptake to Determine the Time-Dose-Fractionation Effect in Radioimmunotherapy

**TO THE EDITOR:** The recent interesting discussion by Rao and Howell (*1*) has introduced the concept of time-dose-fractionation (TDF) into radioimmunotherapy (RIT). In TDF, the absorbed dose rate is considered to be clinically important (*2*). Using theoretical arguments, the authors proposed that TDF be used in both treatment planning and radionuclide selection for RIT. While we agree that TDF is significant in $^{226}$Ra brachytherapy (*2*), we feel that Rao and Howell may not have justified its inclusion in beta-therapy or considered the most general form of the TDF computation needed for a radionuclide source.

Briefly, Rao and Howell (*1*) assumed that a tumor TDF estimate could be done using the simple formula:

$$TDF = 0.122 r_0^{1.35} \tau_e. \qquad \text{Eq. 1}$$

In the above equation, $r_0$ was the "initial" dose rate (cGy/hr) whose exponent (1.35) was an empirical constant previously derived from various clinical brachytherapy trials using $^{226}$Ra sources (*3–5*). The time quoted, $\tau_e$ (days), was an effective time in the tumor given by:

$$\tau_e = T_{e,t} - T_{eu,t}, \qquad \text{Eq. 2}$$

with $T_{e,t}$ being the effective half-life and $T_{eu,t}$ the effective uptake half-time for the lesion. Since such times involve both biological as well as physical decay, the physical half-life of the radionuclide will have an important impact on the TDF estimate (*1*). By comparing various estimated TDF values, the authors argued for using radionuclides with extended physical half-lives in RIT.

Initially, one may question the applicability of TDF concepts developed with a pure photon-emitter such as an encapsulated source of $^{226}$Ra in the RIT context of pure beta sources such as $^{90}$Y or $^{32}$P. A proof of dose rate effects with beta emitters seems necessary, but was not described in tumors by Rao and Howell (*1*).

Two numerical difficulties also occur with the practical use of Equations 1 and 2. Most importantly, it is not clear what rate is to be utilized. In biodistribution studies, absorbed dose rate necessarily begins at zero and goes through a maximum before becoming zero again at long intervals (*6*). The authors (*1*) elected to refer to an "extrapolated" value, apparently meaning something different from the initial or the maximum value of the r(t) curve. Also problematic was the use of a simple time difference, as in Equation 2, to account for the time integration of dose rate.

To eliminate both numerical problems, we suggest that one

**TABLE 1**
Time-Dose-Fractionation Factors (TDFs) for Three Radionuclides

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Yttrium-90 | Condition 1*<br>$T_{e,t}$ = 2.2 d<br>$T_{eu,t}$ = 1.1 d<br>$\tau_{e,t}$ = 1.1 d | | | | | | | |
| $r_0$, Dose rate (cGy/hr) | 2.5 | 5.0 | 10 | 20 | 30 | 40 | 50 | 100 |
| TDF (Ref. 1) | 0.462 | 1.21 | 2.97 | 7.7 | 13.2 | 19.58 | 26.4 | 67.32 |
| TDF (This work) | 0.320 | 0.817 | 2.08 | 5.31 | 9.18 | 13.53 | 18.29 | 46.63 |
| Iodine-131 | Condition 1*<br>$T_{e,t}$ = 5.0 d<br>$T_{eu,t}$ = 1.5 d<br>$\tau_{e,t}$ = 3.5 d | | | Condition 2<br>$T_{e,t}$ = 10.0 d<br>$T_{eu,t}$ = 6.5 d<br>$\tau_{e,t}$ = 3.5 d | | | | |
| $r_0$, Dose rate (cGy/hr) | 2.5 | 5.0 | 10 | 20 | 30 | 40 | 50 | 100 |
| TDF (Ref. 1) | 1.5 | 3.8 | 9.6 | 24.4 | 42.2 | 62.2 | 84.0 | 214.0 |
| TDF (This work, condition 1) | 1.20 | 3.06 | 7.80 | 19.89 | 34.39 | 50.70 | 68.53 | 174.69 |
| TDF (This work, condition 2) | 0.87 | 2.22 | 5.67 | 14.45 | 24.97 | 36.83 | 49.77 | 126.87 |
| Phosphorus-32 | Condition 1*<br>$T_{e,t}$ = 6.9 d<br>$T_{eu,t}$ = 1.6 d<br>$\tau_{e,t}$ = 5.3 d | | | | | | | |
| $r_0$, Dose rate (cGy/hr) | 2.5 | 5.0 | 10 | 20 | 30 | 40 | 50 | 100 |
| TDF (Ref. 1) | 2.23 | 5.83 | 14.31 | 37.1 | 63.6 | 94.34 | 127.2 | 324.36 |
| TDF (This work) | 1.91 | 4.87 | 12.41 | 31.63 | 54.69 | 80.64 | 108.99 | 277.82 |

*Condition 1 is from Ref. 1 and is based on biological rate constants for an unspecified antibody.