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REPLY: We would like to thank Drs. Halpern et al., Law-
rence, the DeNardos, Massuger et al., and Mansi et al. for 
their comments on our recent editorials (1,2). We agree with 
the concepts expressed by Massuger et al. and Mansi et al., 
since they provide additional data in support of our position.

We offer the following reply to the points raised by the 
other correspondents. The terms sensitivity and specificity 
are used in a sense that would imply clinical utility of radioim-
unoimaging. Inspection of the articles cited by Halpern et al. 
and the DeNardos (that have been published in peer 
reviewed journals and refer to data on lesion detection in 
patients) indicates the results of Table 1.

From the data in Table 1, it is clear that some lesions can 
be localized with radioimmunoimaging techniques, however, 
the methodology cannot identify all sites of antigen producing 
documented disease. Although some studies have reported 
sensitivities of >90% for tumor detection this is not the norm. 
In those studies in which large numbers of patients were 
evaluated (melanoma and colorectal carcinoma), sensitivity is 
closer to 70–80%. In a study with PAY-276, for example, a 
total of 11/81 lesions were seen on radioimmunoimaging. 
These findings indicate that the technique may be useful for 
localization of particular types of tumor, but needs further 
development prior to implying that wide application is in 
order.

As suggested by Halpern et al., the case for antimyosin 
imaging is much stronger. For example, overall sensitivity was 
93% in three studies evaluating 132 patients (3,4,5). In a phase

<table>
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<th>TABLE 1</th>
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<td>Lesion Detection with Radioimmunoimaging Techniques</td>
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<td>Primary tumor</td>
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<tr>
<td>Colorectal</td>
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<td>Mab35,Fab</td>
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<td>ZME-018</td>
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<td>ZME-010</td>
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<td>MR-ML-05,Fab</td>
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<td>HMFG2</td>
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<td>PAY-276</td>
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*% of all known lesion sites identified in the radioimmune images; 
†% of known lesions >1.5 cm in diameter; in this study, greater sensitivity was achieved with higher doses of antibody; 
‡Sensitivity of 29% for 2.5 mg of antibody (n = 4) and 74% for 20 mg (n = 6); 
§The false-positive rate in this study was 50%.

**H = reference from Halpern et al. and D = reference from DeNardo and DeNardo.

3 multicenter trial, sensitivity was 94% for 202 patients with transmural infarction and 84% for 57 patients with non-
transmural infarction (6). In the case of radioimmuno imaging for infection, the data are sparse. Similarly, imaging of thombo-
bus also gets mixed reviews.

Concerning the important point raised about the number and 
affinity of binding sites for radioimaging. Dr. Denardo states (7): "In the absence of heterogeneous expres-
sion of the antigen or obstacles to delivery of the antibody to 
the cell membrane antigenic sites, the 107 to 109 antibody 
molecules can be accumulated in 1 gram of cancer tissue." 
This suggests that up to 250 µg of antibody (25% of the 
injected dose after administration of 1.0 mg of antibody) could 
be concentrated in a single gram of tumor. These attractive 
asumptions, unfortunately, have not been borne out by clin-
ical experience. In practice, lesions rarely concentrate more 
than 0.01% of the injected dose.

We agree with the authors that the relative mass of antibody 
administered to a mouse or man is not the sole determinant 
for the different levels of accumulation of radiolabeled anti-
body in tumors in these species. Imaging studies performed 
following radioimmunotherapy, where large amounts of pro-
tein and radioactivity are administered, rarely identify lesions 
that were not seen with smaller diagnostic doses. These obser-
vations do not favor the prospective of Dr. Lawrence that 
scaling the mass and associated radioactivity of an antibody 
preparation to the weight of the subject (mouse versus man) 
would result in similar imaging results. The author's statement 
that "no application of nuclear tracers has consistently demon-
strated a sensitivity significantly greater than 80% in tumor

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imaging at depth and it is unfair to criticize monoclonal usage on the basis of mass differences between species” requires rebuttal. The use of monoclonal antibodies for tumor detection can only be justified if it has greater sensitivity compared to other techniques.

Regarding the “double-edged sword” metaphor, Lawrence is incorrect in his assumption that we were referring to the risk of the human anti-mouse antibody (HAMA) response associated with murine antibodies. Rather it was presented to indicate that while nonspecific accumulation of antibody decreases the specificity of specific antigen-directed imaging, in some cases it can be useful for lesion detection. This contention is supported in the discussion of the potential usefulness of nonspecific accumulation by Dr. Lawrence.

With respect to the HAMA response to intact murine antibody, we disagree with the contention that the effect is independent of mass of carrier injected. While the exact amount of antibody necessary to elicit a significant HAMA response is controversial and probably variable, certain points are clear. In the over 500 patients injected with antimyosin (usual dose ~500 μg), significant HAMA titers were extremely rare even after multiple doses (8,9). In contrast, with the doses of antibody used in most tumor imaging studies, significant HAMA titers are common (10,11). In the extreme case of immunotherapy with OKT3 antibodies in post-transplant patients, significant HAMA levels are almost invariably produced (12,13). We agree with Dr. Lawrence that the use of human antibodies will decrease the HAMA response. However, as suggested by the DeNardos, HAMA is primarily directed against Fc, but has been reported against Fab. Thus, humanized antibodies will not totally eliminate production of these antibodies, as indicated by the high titers of antidiotype antibodies in patients treated with OKT3 antibodies (14,15).

Most of the authors’ comments about antibody fragments for radioimmunoimaging are in general agreement with our editorial. However, they neglect one important fact. While it is true that in many cases, the rapid clearance of antibody fragments from the circulation results in lower absolute lesion concentration of antibody, it also increases target-to-background ratio and thus improves lesion detectability.

We agree that the equilibrium argument presented is an over simplification of the conditions that exist in vivo. However, like others (16) we feel this approach is a useful starting point for further discussion.

We disagree with the contention that even though tumor imaging has not been greatly improved by the use of monoclonal antibodies, the ultimate use of these reagents could well be in radioimmunotherapy. It seems unlikely that an antibody that cannot target enough radioactivity to a lesion for detection can deliver a sufficient dose for treatment.

In conclusion, while antibody imaging for neoplasms is steadily improving, it still suffers from a lack of reliable lesion localization and a lower than predicted concentration of antibody at sites of known lesions. These observations suggest that radioimmunoimaging for tumor detection is not yet ready for widespread patient use. Additional work, identifying the nature of the barriers to effective lesion localization, presents the challenge for the current generation of investigators in this area.

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