Reply

We thank Dr. Marcus for her letter discussing our paper on the labeling of human lymphocytes with indium-111 (*1*). We would like to make the following comments. First, Dr. Marcus quotes a study on the incidence of malignancies in patients who have been treated with I-131 for hyperthyroidism and, consequently, have received thousands of rads. This situation differs in several aspects, however, from the labeling of human lymphocytes with indium-111. It is to be expected that in the case of hyperthyroidism the majority of lymphocytes, which have been irradiated so heavily, can no longer proliferate. In our own experience, most of the lymphocytes irradiated with 2000 rad in vitro are not able to proliferate, even after stimulation with a powerful T-cell mitogen (ALS). In contrast, as we have indicated in the Discussion of our paper, the proliferative capacity of lymphocytes labeled with a high dose of In-111 (15 μCi/10^7 lymphocytes) is still 50% of the control value. As a consequence, it can be expected that cells labeled with much lower doses, carrying some aberrations such as small deletions, will certainly be able to proliferate. In addition, it is not known whether lymphocytes in the thyroid gland participate in recirculation of these cells and, if so, whether they can still encounter antigen in lymphoid organs. In the case of In-111 labeling for lymphocyte-migration studies, lymphocytes themselves are purposely labeled to permit monitoring of their migration through lymphoid organs after reinfusion. Thus, the cells are likely to encounter antigenic stimuli, inducing proliferation. Moreover, the In-111-labeled cells are affected by Auger electrons, because the nuclide is actually brought into the cell. However, although these In-111-labeled lymphocytes can still proliferate in vitro, we must admit that we are not certain about their behavior in vivo.

As a second point, Dr. Marcus questions whether there is a causal relationship between cytogenetic aberrations detected in peripheral-blood lymphocytes and the risk of malignancy. Especially, she downplays the risk of labeling peripheral-blood lymphocytes with indium-111 because stem cells are not directly labeled. Regarding this point, we would like to make two remarks. First, it is known that hemopoietic progenitor cells can circulate in the peripheral blood compartment [about 0.1 to 0.2% of mononuclear cells in the periphery (*2*)]. Second, it may be mentioned that in atomic-bomb survivors an increased risk of not only myeloid but also lymphatic malignancies has been observed, namely, acute lymphatic leukemia, malignant lymphoma, and multiple myeloma (*3–5*). The existence of these types of tumors might suggest that not only stem cells but also more mature cells may degenerate into malignant proliferation. Moreover, the latter did not become apparent until 20 yr or more after exposure. As a consequence, the argument of Dr. Marcus regarding the risk of developing blood-cell malignancies in patients with hyperthyroidism does not hold, because the follow-up period was not long enough. Thus, in our opinion, chromosomal aberrations (especially when involving the sites in which oncogens are located) in peripheral-blood lymphocytes do carry a risk.

"A relatively practical experiment," as suggested by Dr. Marcus, will be rather difficult. An essential part of such an experiment would be to assess the proliferative capacity of these cytogenetically damaged lymphocytes. Because this cannot be performed on biopsy material, one would need peripheral blood lymphocytes. The chance of picking up these lymphocytes in peripheral blood—if they circulate at all—is extremely small.

In conclusion, in our opinion we may neither conclude that the use of indium-111 as a label for peripheral-blood cells is extremely dangerous nor can we conclude that it is safe. We do not agree with Dr. Marcus, who states that the risk is extremely small and "therefore not important," because the risk is difficult to assess without appropriate survey of patients who have been exposed to indium-111. We think this method may not be applied for the study on recirculation of lymphocytes in healthy individuals. Before appropriate follow-up studies have been performed in patients who have received In-111-labeled cells in the past, the risk of this labeling procedure in diagnostic use must be weighed against the risk of the disease for which this procedure is applied.

R. J. M. TEN BERGE
P. TH. A. SCHELLEKENS
Central Laboratory of the Netherlands
Red Cross Blood Transfusion Service
Amsterdam, The Netherlands
A. T. NATARAJAN
University of Leiden
Leiden, The Netherlands
M. R. HARDEMAN
E. A. VAN ROYEN
University Hospital Wilhelmina Gasthuis
Amsterdam, The Netherlands

REFERENCES

1. TEN BERGE RJM, NATARAJAN AT, HARDEMAN MR, et al: Labeling with indium-111 has detrimental effects on human lymphocytes: Concise communication. *J Nucl Med* 24:615–620, 1983
2. RUBIN SH, COWAN DH: Assay of granulocytic progenitor cells in human peripheral blood. *Exp Haemat* 1:127, 1973
3. ISHIMARU T, HOSHINO T, ICHIMARU M, et al: Leukemia in atomic bomb survivors, Hiroshima and Nagasaki, 1 October 1950–30 September 1966. *Radiat Res* 45:216–233, 1971
4. NISHIYAMA H, ANDERSON RE, ISHIMARU T, et al: The incidence of malignant lymphoma and multiple myeloma in Hiroshima and Nagasaki atomic bomb survivors, 1945–65. *Cancer* 32:1301–1309, 1973
5. ISHIMARU M, ISHIMARU T, MIKAMI M, et al: Multiple myeloma among atomic bomb survivors in Hiroshima and Nagasaki, 1950–76: Relationship to radiation dose absorbed by marrow. *J Natl Cancer Inst* 69:323–328, 1982