Decades of careful experimentation have established that the intrinsic radiosensitivity of tumor cells is a major determinant of the radiation response of tumors, with modifying contributions of extrinsic factors such as the tumor microenvironment and host immune response. The publication by Garcia-Barros et al. (1) proposes a new paradigm in which host endothelial cell killing by radiation is the major factor determining tumor response at doses comparable to those used in radiotherapy.

To claim such an extraordinary shift in paradigm places a burden to provide extraordinary evidence. However, we believe that the data provided by Garcia-Barros et al. (1) fall short of that standard. Of concern is the fact that the tumors used in this study grew unexpectedly slowly in the wild-type littermates of the acid sphingomyelinase (asmase) knockout mice. This raises the possibility that the tumor–host relationship may be unusual in this system. Innate-immune mechanisms, acquired-immune mechanisms, or both may be operating that cause tumor cell death and predispose the endothelial cells to apoptosis, which may not occur with nonimmunogenic tumors growing in syngeneic or autologous conditions. This view is supported by the finding that 50% of asmase<sup>++</sup> mice were cured of 100 to 150 mm<sup>3</sup> MCA/129 tumors by the unusually low radiation dose of 15 grays (Gy) [50% tumor control (TCD<sub>50</sub>).] Typical TCD<sub>50</sub> values for similar-sized tumors exceed 30Gy, with immunogenic tumors showing greater sensitivity (2). If host infiltrating cells were exceptionally active in the tumor–host combination used in this study, as we suspect, the results would be biased in favor of finding a difference between the asmase<sup>−/−</sup> and asmase<sup>++/++</sup> mice, because the ceramide pathway is known to be important in tumor necrosis factor–α (TNF-α) and interferon-γ (IFN-γ) signaling, cytokines that would be expected to be involved in mediating the observed effects.

In light of these concerns, it would be premature to declare a paradigm shift in our understanding of radiation therapy. Although the Garcia-Barros et al. study (1) is important and provocative, further work with other systems is needed to determine the contribution of endothelial cell response to the therapy of human tumors.

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17 June 2003; accepted 30 October 2003
Comment on "Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptosis" (II)
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Science 302 (5652), 1894.
DOI: 10.1126/science.1089517