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Letter to the Editor

Correspondence re: E. H. Perkins and L. H. Cacheiro. Immunodepression, a Noncontributor to Radiation-induced Leukemogenesis of the RFM Mouse. Cancer Res., *40:* 357–361, 1980.

In a recent report, Perkins and Cacheiro (4) concluded that immunosuppression was a "noncontributor" in radiation leukemogenesis in the RFM mouse. This conclusion was based on the observation that postirradiation injection of syngeneic spleen cells hastened the recovery of the ability of irradiated mice to respond immunologically to sheep RBC or allogeneic tumor cells but did not alter the rate of development or the final incidence of induced thymic lymphomas. Since Perkins and Cacheiro assumed that the thymic lymphoma incidence should have been reduced in these mice if immunosuppression played a role in radiation leukemogenesis, they argue that our proposal (1–3, 5), "the radiation leukemogenic mechanism involves suppression of the ability of irradiated animals to cope with the malignantly transformed cells or the viruses which induce these cells," is unwarranted (4). As outlined below, the inability of these authors to demonstrate an effect of spleen cell reconstitution on thymic lymphoma patterns was predicted by our original studies (1–3, 5), and their expectation of positive effects resulted from a misinterpretation of our data.

What our experiments (1–3, 5) purported to show was: that the hyaline-like material which accumulates in the kidney of glomerulosclerotic mice contains complexes of murine leukemia virus antigens and specific antibody directed against them; that animals which developed the severe form of glomerulosclerosis suffered a lesser risk of developing thymic lymphoma (and other leukemias) relative to their age-matched but nonglomerulosclerotic counterparts; and that radiation doses of 200 rads or more suppressed the development of glomerulosclerosis.

Somehow, Perkins and Cacheiro (4) interpreted our results as suggesting that immunosuppression makes a major contribution to the final incidence of thymic lymphoma when, in fact, the exact reverse is true. In our original studies (Ref. 1; Tables 2 and 3), 311 unirradiated mice were examined histologically, and 114 or 36.6% were found to have the severe form of glomerulosclerosis. We projected the rates of thymic lymphoma development observed in nonglomerulosclerotic mice on this population of 114 and estimated that 14.8 cases of thymic lymphoma should have been observed if the glomerulosclerotic mice were as sensitive as were the nonglomerulosclerotic mice to the development of thymic lymphoma. Instead, only 4 cases were observed, meaning that the unfettered operation of our proposed immunological defense mechanism had produced only a 3.5% (10.8/311) reduction in thymic lymphoma incidence.

The same pattern was observed in our analysis of 1274 irradiated mice. In the 386 glomerulosclerotic mice observed, we expected 54.3 cases of thymic lymphoma but observed 26 cases. Therefore, residual immunological defenses produced a 2.2% (28.3/1274) reduction in the incidence of thymic lymphoma. If we correct the data for the inhibition of glomerulosclerosis development (36.6% in control and 30.3% in irradiated mice) by switching 80 mice from the higher-risk nonglomerulosclerotic to the lower-risk glomerulosclerotic category, we are, in essence, simulating the spleen cell reconstitution study of Perkins and Cacheiro (4). This procedure reduces the observed incidence of thymic lymphoma from 11.8 to 11.4%.

Even if we consider the 300-rad dose level only, which was used by these authors, it is obvious that the expected alteration in the final incidence of thymic lymphoma is small, 2.3%. With the sample sizes used by Perkins and Cacheiro (4), our results predict that spleen cell reconstitution should have saved less than one mouse from thymic lymphoma. We suggest that larger sample sizes will be necessary if spleen cell reconstitution experiments are to be used to test our proposal.

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Our conclusion (7) that immunodepression did not contribute to the early inductive events in radiation leukemogenesis was based on our 2 observations: (*a*) injection of bone marrow cells failed to alter measured immunological indices but protected the host, demonstrating that factors other than immunodepression were of primary significance in the inductive process; and (*b*) although spleen cell injection enhanced immune competence, it failed to reduce the high incidence (>60%) of thymic lymphoma.

Contrary to Yuhas' suggestion in his letter to the editor, our intent was not to test his proposal (2, 8), nor did we interpret Yuhas' data as "suggesting that immunodepression makes a major contribution to the final incidence of thymic lymphoma." Our review of the original data of Clapp *et al.* (1), which

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