To the Editor:

This concerns the valued review article by Martin J. Cline in the November 1, 1994 issue of Blood on histiocytes and histiocytosis, in which he divides the histiocytic disorders in four major categories: (1) reactive macrophage histiocytoses, (2) malignant macrophage histiocytoses, (3) reactive Langerhans cell histiocytosis (LCH), and (4) malignant LCH. We would like to point out that Cline’s classification is different from that adopted in 1987 by the Histiocyte Society. This international body of clinicians, pathologists, and laboratory scientists outlined the morphologic, immunohistochemical, and clinical criteria required for the diagnosis of histiocytic disorders in children. The various entities were grouped as follows: LCH as class I, histiocytoses of mononuclear phagocytes other than Langerhans cells as class II, and malignant histiocytic disorders as class III (Table 1). The society hoped its classification would be widely adopted and thus promote the benefits of coherent communication between physicians and laboratory investigators and permit accurate comparison of clinical data. These aims are being realized, for example, in the case of the ongoing large-scale cooperative international studies of the natural evolution of LCH and its response to treatment.

We also would like to expand on Cline’s “note added in proof.” For decades it has been thought that LCH is a reactive proliferation rather than a neoplastic process. However, recent laboratory studies have shown that the cells in some forms of LCH are clonal expansions. The implications of these reports remain to be defined. On the one hand, the findings are compatible with the hypothesis that LCH is a clonal neoplastic disorder arising from somatic mutations. On the other hand, clonal proliferation of rare progenitor cells resident or attracted into lesions in response to cytokines may produce a nonneoplastic clonal proliferation of histiocytes. “Clonality,” therefore, does not necessarily indicate a malignant process, because clonal cells have been detected in several disorders that are not malignant. Although these issues are being resolved, physicians should be cautioned against assuming that LCH has been shown to be a form of cancer. The interested reader is invited to read the issue of the British Journal of Cancer (70; Supplement XXIII, 1994) that is devoted to LCH. It contains several reports that pertain to the possible etiologies of LCH including those relevant to clonality.

Table 1. Classification of Histiocytosis Syndromes in Children

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>Class I</td>
<td>Langerhans cell histiocytosis</td>
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<td>Class II</td>
<td>Histiocytosis of mononuclear phagocytes other than Langerhans cells</td>
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<td></td>
<td>Hemophagocytic lymphohistiocytosis (familial and reactive)</td>
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<td></td>
<td>Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman)</td>
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<td>Juvenile xanthogranuloma</td>
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<td>Reticulohistiocytoma</td>
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<td>Class III</td>
<td>Malignant histiocytic disorders</td>
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<td></td>
<td>Acute monocytic leukemia (FAB M5)</td>
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<td></td>
<td>Malignant histiocytosis</td>
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<tr>
<td></td>
<td>True histiocytic lymphoma</td>
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REFERENCES
An international histiocytic language [letter; comment]

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