

# This Week's Citation Classic®

**Boggs D R, Wintrobe M M & Cartwright G E.** The acute leukemias: analysis of 322 cases and review of the literature. *Medicine* 41:163-225, 1962.

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All patients with acute leukemia (AL) at the University of Utah from 1944 to 1960 were reviewed and a comprehensive picture of AL was constructed. Various hypotheses were tested; lymphoblastic and myeloid AL were different diseases; concentration of blasts in blood predicted survival but had little relation to other manifestations. [The SCI® indicates that this paper has been cited in over 240 publications.]

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This paper is still consulted as an exhaustive source of clinical data. For example, in a recent review of diseases associated with marked eosinophilia, the only data I could find for eosinophils in the acute leukemias (AL) were my own.

As a clinical associate at the National Cancer Institute (NCI), I saw many patients with acute leukemia, helped analyze all patients seen there,<sup>1</sup> and used the superb library to review all of the Cumulative Indexes and the precursors of this publication (1879 to 1958) under the heading of leukemia. The last comprehensive monograph on AL was that of Forkner, 1938.<sup>2</sup> I decided to try to write such a monograph and collected the patient data and completed the literature review and the paper while a clinical fellow in hematology.

At that time there were two schools of thought as to how one should classify patients with AL: by simply denoting that the patient was a child or an adult, or by the cell type of the blasts as examined in stained smears. Many hematologists had (and have) serious doubts that a cell type could be reliably assigned to many cases in which the leukemic cells (blasts) had few morphologic features of differentiation.

I tested the ability of Wintrobe, Cartwright, and myself to distinguish between the general categories in the following manner. They had a comprehensive slide file on all patients that they had seen. I reviewed these without knowledge of the original diagnosis, forcing myself to make a choice between acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML). In cases of disagreement (3 percent), Wintrobe and Cartwright reviewed the

slides. The response of ALL and AML to adrenal-gluco-corticosteroids (steroid) was then examined. Earlier, Roger Lester and I had written a manuscript showing that children with AML at the NCI had not responded to steroids (nor to methotrexate), agreeing with one large study.<sup>3,4</sup> Our NCI superiors were not sure there was a difference in therapeutic response between ALL and AML and would not allow us to submit the paper for publication. None of 50 patients with AML at Utah had achieved a remission on such therapy and only one had objective improvement; my mentors had abandoned such therapy. In contrast, 100 with ALL had a 71 percent remission rate and 91 percent at least improved. Yet a significant number of AML patients still receive large doses of this very toxic form of therapy.

Except for some minor clinical differences, all morphologic varieties of AML seemed to behave in pretty much the same fashion. The clinical manifestations and response to therapy in AML were quite similar in adults and children, and this has remained the case in subsequent studies.<sup>5</sup> The lesser rate of remission induction in the aged reflects a higher death rate during remission induction rather than any difference in the disease. In ALL, response to therapy was not as good in adults as in children, but in other respects the disease appeared to be the same in adults and children. Thus the hypothesis, which suggested that a practical, working classification for AL was to simply divide such patients into adults and children, ignoring cell type, seemed to be negated. Subsequent data have indicated that the target cell in AML is usually a stem cell that is pluripotent for all of the above cells, but not for lymphocytes. Thus, considering most cases of AML to be part of the spectrum of a single disease with differing phenotypic expression of cellular morphology becomes a logical as well as a viable hypothesis.<sup>5</sup>

I suspect a principal reason that this paper has been cited so frequently may simply be that an extraordinarily large number of papers dealing with various clinical aspects of AL are published each year. The details of therapy as outlined in 1961 are not at all applicable today, but the general principles remain pretty much unchanged: induce a complete remission, give maintenance therapy after remission induction, and hope for a cure.

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