

# This Week's Citation Classic®

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**Boggs D R.** Hematopoietic stem cell theory in relation to possible lymphoblastic conversion of chronic myeloid leukemia. *Blood* 44:449-53, 1974.  
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The hypothesis that chronic myeloid leukemia (CML) could terminate in lymphoblastic leukemia represented a melding of clinical observation with knowledge of murine hematopoietic stem cells (HSC). Now supported by extensive data, it makes sense if the CML target is an HSC totipotent for lymphoid and myeloid tissue. [The *SCI*® indicates that this paper has been cited in over 225 publications.]

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In 1972 I was at a meeting of the American Society of Hematology and chatting casually with a few other clinical investigators. I raised the possibility that chronic myeloid leukemia (CML) might terminate in a blastic crisis characterized by a morphologic appearance and therapeutic response resembling acute lymphoblastic leukemia (ALL), rather than the well-recognized phase resembling the acute myeloblastic leukemias (AML). I based my argument on the morphologic appearance of the immature cells seen in a few patients, the response of one to prednisone alone, a report that approximately one-third of patients in blast crisis of CML had responded to a regimen of prednisone and vincristine,<sup>1</sup> and also upon data indicating that there was a hematopoietic stem cell in the mouse that could produce lymphoid as well as myeloid tissue.<sup>2</sup>

Fred Stohlman had joined our group and abruptly entered the conversation with: "Write me an editorial!" I demurred and he persisted: "and relate it to stem cell theory!" Fred, as anyone with even a vague interest in hematology should know, was a Big man. Big in his knowledge, scientific acumen, training of new investigators, editorship of *Blood*, humor, warmth, and in person, being 6' 7-1/2" tall. Many of us were assigning him the role of "Mr. Hematology" before a bomb blew him, his wife, and fellow passengers from the air and into the bay of Athens in 1974. I chose to consider a repeated request from Fred to be a demand.

Near the close of this editorial I wrote: "The hypothesis that lymphoblastic conversion of CML may occur is based on what many will consider to be

highly questionable data, appearance of blasts in Wright's-stained smears." Some consider "morphology" to be more an art than a science, but I disagree. However, there is no question that classifying immature blasts with no cytoplasmic clues as myeloblasts or lymphoblasts requires both extensive experience in being forced to make such a choice and a strong interest in being able to do so. Nonetheless, since 1900 when Naegeli first described the myeloblast,<sup>3</sup> many have indicated their disbelief in the accuracy of such distinctions and have adopted terms such as "undifferentiated" or "stem cell" leukemia for those cases with cells with minimal features of differentiation.

Distinguishing ALL from AML on the basis of response to specific forms of therapy has also been disputed by many. I had gained confidence in such distinctions since Maxwell M. Wintrobe, George E. Cartwright, and I had been able to equate steroid response with what we considered to be lymphoid morphology with greater than 0.95 probability.<sup>4</sup>

The chief "hooker" in my hypothesis was the presence of the Ph<sup>1</sup> chromosome in all myeloid cells in patients with CML and its absence in lymphocytes. (Subsequently, the Ph<sup>1</sup> has been noted occasionally in lymphocytes, but even more intriguing are observations suggesting that this chromosome abnormality is absent in some cells that are nonetheless in the CML clone.)<sup>2</sup>

This hypothesis was not universally popular. Before publication of the editorial, I included it in a textbook chapter, a section promptly deleted by the book's editor. I was chided from the lectern for working from inadequate data, even when the now-famous speaker presented data tending to further support the hypothesis. Hypotheses are useful only if they can be subjected to scientific scrutiny.

While the manuscript was in press, I received a call from Ronald McCaffrey, who was delighted with the idea. Ron, now chief of hematology-oncology at Boston University, was working with David Baltimore at MIT and studying cells from patients with leukemia for the presence of terminal deoxynucleotidyl transferase (TdT). This enzyme was then thought to be found exclusively in cells of lymphoid lineage, but he had found it in cells of a patient with CML in blast crisis. He had presented his data at a seminar attended by Fred, who had shared a preprint with him.

Why has this editorial been cited frequently? It seems to me that hypotheses are likely to be mentioned for one of two reasons: they are so outlandish that they gain fame even after they are disproven or they gain widespread acceptance when subsequent experiments fail to disprove them, particularly when they seem to make sense of otherwise seemingly disparate data.

1. Canellos G P, DeVita V T, Whang-Peng J & Carbone P P. Hematologic and cytogenetic remission of blastic transformation in chronic granulocytic leukemia. *Blood* 38:671-9, 1971. (Cited 170 times.)
2. Flalkow P J. Clonal and stem cell origin of blood cell neoplasms. (Lobue I, Gordon A S, Silber R & Muggia F M, eds.) *Contemporary hematology/oncology*. New York: Plenum Press, 1980. Vol. I, p. 1-46.
3. Naegeli O. Ueber rothes Knochenmark und Myeloblasten. *Deut. Med. Wochenschr.* 26:287-90, 1900.
4. 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. (Cited 220 times.)

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