

## The first achievement of complete remission in childhood leukemia by treatment with the folic acid antagonist aminopterin

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**TITLE** Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin).

**AUTHORS** Farber S, Diamond LK, Mercer RD, Slyvester RF Jr, Wolff JA.

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These days almost 90% of children with acute lymphoblastic leukemia and 70% of those with acute myelogenous leukemia are cured. The first significant step towards these results was published by Dr. Sidney Farber and colleagues 74 years ago.<sup>1</sup> Their achievement was preceded by a devastating failure. Following the great success of treatment of folate deficiency by conjugates of folic acid, and given the morphological similarity between megaloblastic anemia and leukemia, Dr. Farber attempted to treat children with leukemia with folate conjugates. Remarkably, he was perceptive enough to note that treatment with folates had the opposite outcome from that desired: it markedly accelerated the leukemias, as he observed both clinically and in postmortem examinations.<sup>2</sup> These observations led him to conduct a clinical trial with the newly synthesised anti-folate, amiopterin;<sup>3</sup> the results were published on June 3, 1948 in the *New England Journal of Medicine*.<sup>1</sup> Sixteen children with leukemia were treated with aminopterin, ten entered transient remissions characterized by a reduction or even complete disappearance of blasts from peripheral blood and bone marrow with recovery of normal hematopoiesis (Figure 1, from the original article). These hematologic findings were accompanied by resolution of the clinical symptoms, regression of hepatosplenomegaly and, in

one case, regression of subcutaneous nodules that were presumed to be leukemic. The major toxicity was “severe stomatitis” and, in one case, pancytopenia and empty bone marrow, for which therapy with liver extracts was attempted. The longest complete remission off therapy was 47 days.

Fast-forwarding to our times, methotrexate is one of the cornerstones of treatment of acute lymphoblastic leukemia. Severe mucositis is indeed one of the major toxicities and folate, in the form of leucovorin, is the main rescue treatment after therapy with high-dose methotrexate. The remarkable observation by Dr. Farber that folate conjugates accelerate leukemia growth serves as an important reminder that vitamins and nutritional supplements, given with the intention to “strengthen the patient”, may fuel a tumor. Cancer and normal cells compete for the same resources with the former being more dependent on the essential fuel. Treatment with L-asparaginase followed the introduction of anti-folates as an effective means to starve tumor cells. Interestingly, controlled calorie restriction has recently been shown to further improve the rate of molecular remission of children with acute lymphoblastic leukemia and is now being tested in a large clinical trial funded by the National Institutes of Health.<sup>4</sup>

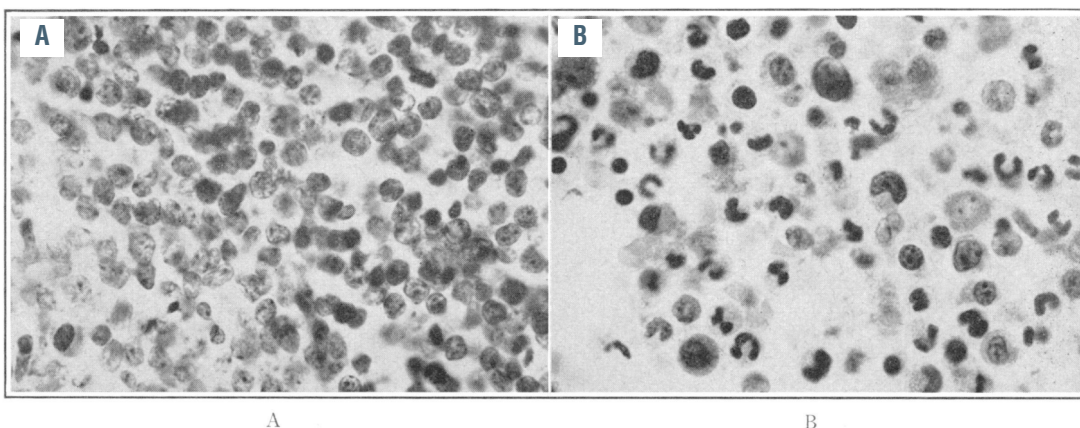


Figure 1. A reproduction of the original figure from the paper in the *New England Journal of Medicine*<sup>1</sup> demonstrating the morphology of the bone marrow before (A) and after 1 month of treatment with aminopterin and crude liver extract (B).

### References

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