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This Week's Citation Classic™

Farber S, Diamond L K, Mercer R D, Sylvester R F, Jr. & Wolff J A. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). *N. Engl. J. Med.* **238**:787-93, 1948.
[Harvard Med. Sch., and Div. Laboratories and Research, Children's Med. Ctr., Boston, MA]

This paper reported the first use of a folic acid antimetabolite in the treatment of children with acute leukemia. A remission was produced in 10 of 16 patients. Details and charts on five cases were given. In a uniformly fatal disease such as this, encouragement was thereby offered. [The *SCI*® indicates that this paper has been cited in over 395 publications since 1955.]

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Methotrexate, a synthetic anti-folic acid compound, is probably the most widely used chemotherapeutic agent for malignancies today.[1] Its trial, in 1948, was the logical outgrowth of the interest in folic acid (pteroylglutamic acid) as a stimulant to cell proliferation. In the mid-1940s, several papers reported that a "folic acid concentrate" inhibited the growth of sarcomas and caused regression of some spontaneous breast cancers in mice treated with intravenous injections of this material. This work could not be substantiated, but it aroused considerable interest in the role of folic acid. Stimulated by these observations, the late Sidney Farber, pathologist at the Boston Children's Hospital, embarked on a trial of folic acid conjugates in a wide variety of malignancies. The folic acid was supplied by Y. SubbaRow, a professor of biochemistry at Harvard Medical School and, later, research director at Lederle Laboratories, who had originally synthesized folic acid and was actively engaged in studying several of its conjugates. Farber, with the cooperation of his surgical and medical associates at several Boston hospitals, treated 90 patients having some two dozen different malignancies.[2] The results were unsatisfactory, but some of the tumors showed accelerated growth of malignant cells and then retrogression, possibly due to outgrowing their blood supply and then suffering from folic acid deficiency. In 1947, SubbaRow, Hutchings, and their associates synthesized pteroylaspartic acid, an antagonist to pteroylglutamic acid (folic acid) and proved, both *in vitro* and in chicks, that there was interference with folic acid metabolism and with the normal growth of cells.[3] This suggested that a folic acid antagonist might be of value in patients with rapidly growing malignant disease, and we persuaded SubbaRow to synthesize several additional folic acid antagonists for human trials. Children with acute leukemia were frequently seen by us, and permission was obtained to try parenteral antifolates in patients in the terminal stages of their disease.

Sixteen children were begun on treatment with parenteral antifolates. Six did not respond at all, but 10 showed definite benefit. The five who had the best results were selected for report in this paper published in the *New England Journal of Medicine* in June 1948. The drug finally utilized in this series of patients was aminopterin, a powerful antagonist of folic acid. Because of troublesome toxic reactions, seen chiefly in the mouth and in the intestinal tract where hemorrhages occurred frequently, another less toxic antifolate called amethopterin, later named "methotrexate," supplied by SubbaRow, was tried and found to be safer and more effective. Unfortunately, SubbaRow succumbed to a heart attack in 1948, so that no other nontoxic antifolates could be tried. In the following year or two, dozens of children with acute leukemia were treated with parenteral methotrexate, and many of them developed remissions one or more times. The burden of treating and following these patients carefully was borne by our assistants, Robert Mercer, Robert Sylvester, and James Wolff.

While methotrexate is not the dreamed-of "magic bullet" for cancer, it nevertheless pushed medical research onto the road toward chemotherapy for malignant disease. This drug continues to be very useful worldwide, alone or combined with other antimetabolites and cell destroyers. It has proved to be an important means of therapy not only for a variety of malignancies but even for nonmalignant diseases such as psoriasis, rheumatoid arthritis, and other conditions. It has continued to be of prime importance as an antimetabolite both by itself and in combination for over 30 years.

Our paper was the oldest article listed in a recent study of 100 classics from the *New England Journal of Medicine*.[4] Between 1948 and 1955 (the first year for which citation data are available in the *SCI*), the number of citations can only be judged by the hundreds of reprints that were requested, showing the paper had achieved considerable popularity.

1. **Jolivet S, Cowan K H, Curt G A, Clendenin N J & Chabner B A.** The pharmacology and clinical use of methotrexate. *N. Engl. J. Med.* 309:1094-104, 1983.
2. **Farber S, Cutler E C, Hawkins J W, Harrison J H, Pierce E C & Lenz G G.** The action of pteroylglutamic conjugates on man. *Science* 106:619-21, 1947.
3. **Hutchings B L, Mowat J H, Oleson J J, Stokstad E L R, Boothe J H, Waller C W, Angier R B, Semb J & SubbaRow Y.** Pteroylaspartic acid, an antagonist for pteroylglutamic acid. *J. Biol. Chem.* 170:323-8, 1947.
4. **Garfield E.** 100 classics from the *New England Journal of Medicine*. *Current Contents* (25):3-10, 18 June 1984.

