

EDITORIAL

THE USE OF FOLIC ACID ANTAGONISTS IN ACUTE LEUKEMIA

ACUTE leukemia remains the most important single problem in the field of hematology. Hopes that the disease may ultimately be controlled have recently been revived. It was found by several groups of investigators that folic acid and its conjugates at times seemed to accelerate the leukemic process.^{1, 2, 3} For this reason, the use of antagonists of folic acid suggested itself as a possible therapeutic measure and several of these have been prepared by Subbarow and his associates.⁴ By manipulation of the pteroyl glutamic acid molecule, as for example substitution of an NH_2 group for the OH group in the 4 position of the pteridine ring structure, an anti-folic acid preparation, 4-aminopteroyl glutamic acid or *aminopterin* is produced. Farber and his associates found that of the various folic acid antagonists which they tried in acute leukemia, aminopterin was by far the most potent. In a series of 16 cases of acute and subacute leukemia in children, these workers⁵ found that injections of aminopterin regularly resulted in remissions lasting for at least three months in 10 of the cases. The remissions were characterized not only by great subjective and objective improvement but by improvement in red count and in platelets, a virtual disappearance of primitive white cells from the blood, and a considerable improvement in the appearance of the marrow.

Farber's results, which were obtained in children, have not as yet been duplicated in adults. Personal communications from various centers where aminopterin and related drugs are being used indicate that good results have often been disappointing and that reactions such as hemorrhage, aplastic anemia, etc. are common. However, in our own series of 16 adults with acute and subacute leukemia, 4 patients with acute or subacute leukemia have developed clear-cut remissions characterized by subjective improvement, rise in red cells and platelets, disappearance of blast forms from the blood and a distinct improvement of the marrow picture. We have also had a clear-cut remission in one childhood case of two treated. Although these results may be considered as coincidental by some observers, the remission rate in Farber's series of 10 of 16 consecutive cases is far beyond the spontaneous rate of remission. We have been impressed, therefore, both in our own small series of cases and through examination of Farber's data, that the factor of spontaneous remission can be completely ruled out. If this is the case, then we may indeed be approaching the future control by chemotherapeutic means of what is now a practically hopeless disorder. The therapeutic effect of anti-pteroylglutamic acid preparations indicates that PGA may be one of the materials concerned in the growth processes of the white cells of leukemia. What is even more likely is that other enzymes more important than PGA are necessary for leukocytic growth. When these are found, anti-enzymes may then be discovered. Certainly further work along these lines is indicated.

Aminopterin and related drugs must be used with great caution for they cause

severe reactions of the mucous membranes and, in large doses, of the marrow as well. These chemicals should by no means be considered as cures; all they apparently do, even in the most favorable cases, is to keep the "flame" of leukemia under temporary control. However, the knowledge that even a little something can be accomplished in acute leukemia is very heartening news indeed, and a great stimulus for continued investigation.

REFERENCES

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- ⁴ SMITH, J. M., JR. ET AL.: *Tr. New York Acad. Sc. Special Number, Series II, 10: 82, 1948.*
- ⁵ FARBER, SIDNEY ET AL.: *New England J. Med.* 238: 787, 1948.

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