FOLIC ACID ANTAGONISTS IN THE TREATMENT OF ACUTE AND SUBACUTE LEUKEMIA

By William Dameshek, M.D., Milton H. Freedman, M.D., and Lester Steinberg, M.D.

In 1947, Martin and co-workers described an impure compound, "7 methyl folic acid," as "displacing" the growth promoting action of pteroyl glutamic acid (PGA) for *Streptococcus faecalis* R. Using a preparation, "X-methyl PGA," prepared by Smith and Hultquist by a somewhat similar reaction, Franklin, Stokstad, and Jukes in the same year found that when it was fed to rats, mice and chicks, an acute deficiency syndrome was produced which was reversed by increasing the dietary level of PGA. They suggested that the preparation might be used to modify certain blood dyscrasias marked by leukocytosis because in rats the white count fell to exceedingly low levels.

The synthesis of 4-amino PGA (aminopterin) was described by Seegers, Smith and Hultquist. This compound was found to be the prototype of a new series of antagonists, which are characterized by high potency, marked clinical effects, toxicity and limited or no reversibility by PGA.

Farber and his co-workers began the use of certain of these compounds in the treatment of acute leukemia in children. The first available compounds were pteroylaspartic acid and methyl pteroic acid, which they believed helped to prolong the lives of a few children. Beginning in November 1947, 4-amino pteroyl glutamic acid (aminopterin) became available, and the first impressive remissions in the course of acute leukemia were produced by the use of this drug.

Our interest in this chemical came about through our previous work with the nitrogen mustards, urethane, and other chemical agents in leukocytic proliferations, as well as in a growing conviction that chemotherapy in these conditions offered the greatest promise for their future control. From April 1948 to June 1949 we treated 40 cases of acute and subacute leukemia with one or more of the folic acid antagonists. Of these 40 cases, 34 were in adults and 6 in children. Eight patients died within one week and therefore cannot be considered as having received an adequate therapeutic trial of the drugs. Of the remaining 32 cases, 27 were in adults and 5 in children.

Except in three instances, all cases were observed at either the J. H. Pratt Diagnostic Hospital, the Boston Floating Hospital, the West Roxbury Veterans Hospital, or the Murphy General Hospital.

One of the cases classified as acute myelocytic leukemia occurred as the end
result of chronic myelocytic leukemia ("myeloblast crisis"). This is probably the first such reported case showing a definite although temporary remission following the use of folic acid antagonist therapy.

**Drugs Used and Methods of Therapy**

The folic acid antagonists used were 4-amino pteroyl glutamic acid (aminopterin), 4-amino-\textsuperscript{N}\textsuperscript{10}methyl pteroyl glutamic acid (\textit{a}-methopterin), 4-amino pteroyl aspartic acid (aminofol), and 4-amino-9 methyl pteroyl glutamic acid (\textit{a}-ninopterin) (fig. 1).

![Chemical structures of folic acid and its conjugates](image)

As to their relative effectiveness, aminopterin was given in a dosage of 1-4 mg. daily, \textit{a}-methopterin 2-5 mg. daily, \textit{a}-ninopterin 5-15 mg. daily, aminofol 25-75 mg. daily, with the dosage varying according to the age and white blood count. For maintenance therapy, aminopterin 0.25 to 1 mg. daily, and \textit{a}-ninopterin 5-10 mg. daily were used. Optimal maintenance doses of 0.5 mg. aminopterin daily for adults and 0.15 mg. daily for children have been worked out. Both aminopterin and \textit{a}-ninopterin were given by mouth as well as by injection; oral administration was as effective, mg. for mg., as the parenteral therapy. Scored tablets of aminopterin (1 mg.) and of \textit{a}-ninopterin (5 mg.) were particularly useful for maintenance therapy.

The various chemicals used in the study were dissolved in sterile normal salt solution and injected intramuscularly daily until a toxic or pronounced hematologic reaction occurred, as evidenced chiefly by a drop in the white cell count, following which the drug was discontinued. The time period and the dosage of drug given before discontinuance varied with each case. Usually the drug was discontinued after five days to three weeks, upon the appearance of a toxic reaction. After the reaction had subsided...
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Type</th>
<th>Antigen Subtype</th>
<th>Initial W.B.C.</th>
<th>Initial Platelets</th>
<th>Drug or Drugs Used</th>
<th>Total Dosage and Days of Administration Before Remission</th>
<th>Time after Therapy Began Complete Remission Estab.</th>
<th>Duration of First Remission</th>
<th>No. of Relapses</th>
<th>No. of Remissions Following Relapse</th>
<th>Other Treatment</th>
<th>Present Status Including Total Duration after Therapy Began (as of June 1, 1949)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, J.C.</td>
<td>3</td>
<td>M</td>
<td>Lymph.</td>
<td>S</td>
<td>8,400</td>
<td>21,000</td>
<td>Aminopterin A-methopterin A-methopterin</td>
<td>8 mgm—4 days 4 mgm—2 days 4 mgm—4 days</td>
<td>30 days</td>
<td>29 days</td>
<td>3</td>
<td>2</td>
<td>Transf. p.r.n. Antibiotics</td>
<td>Deceased—8½ months.</td>
</tr>
<tr>
<td>6, E.D.</td>
<td>52</td>
<td>M</td>
<td>Lymph.</td>
<td>S</td>
<td>2,800</td>
<td>360,000</td>
<td>Aminopterin</td>
<td>22 mgm—14 days</td>
<td>20 days</td>
<td>Still present</td>
<td>No definite</td>
<td>Initial remission still present</td>
<td>&quot;</td>
<td>Living—14 months</td>
</tr>
<tr>
<td>7, E.W.</td>
<td>45</td>
<td>M</td>
<td>Lymph.</td>
<td>S</td>
<td>3,300</td>
<td>124,800 (drop before admission)</td>
<td>Aminopterin</td>
<td>14 mgm—7 days</td>
<td>26 days</td>
<td>5.5 months</td>
<td>1</td>
<td></td>
<td>&quot;</td>
<td>Deceased—9½ months</td>
</tr>
<tr>
<td>17, K.B.</td>
<td>29</td>
<td>F</td>
<td>Lymph.</td>
<td>S</td>
<td>365,000</td>
<td>10,000</td>
<td>Aminopterin</td>
<td>15 mgm—7 days</td>
<td>17 days</td>
<td>3.5 months</td>
<td>2</td>
<td>1</td>
<td>&quot;</td>
<td>Deceased—6 months (Typhoid meningitis also)</td>
</tr>
<tr>
<td>19, J.U.</td>
<td>59</td>
<td>M</td>
<td>Unclassified</td>
<td>S</td>
<td>2,400</td>
<td>50,000</td>
<td>Aminopterin</td>
<td>26 mgm—21 days</td>
<td>20 days</td>
<td>3 months</td>
<td>1</td>
<td></td>
<td>&quot;</td>
<td>Deceased—5½ months</td>
</tr>
<tr>
<td>23, A.M.</td>
<td>18</td>
<td>M</td>
<td>Myel.</td>
<td>A</td>
<td>49,500</td>
<td>22,000</td>
<td>Aminopterin</td>
<td>19 mgm—7 days</td>
<td>19 days</td>
<td>2.5 months</td>
<td>No definite</td>
<td></td>
<td>&quot;</td>
<td>Deceased—2½ months (Possible reaction to intravenous mycolic)</td>
</tr>
<tr>
<td>25, J.D.</td>
<td>47</td>
<td>M</td>
<td>Myel.</td>
<td>S</td>
<td>4,300</td>
<td>285,000</td>
<td>A-ninopterin</td>
<td>250 mgm—50 days</td>
<td>21 days</td>
<td>Still present</td>
<td>No definite</td>
<td>Initial remission still present</td>
<td>&quot;</td>
<td>Living—7½ months</td>
</tr>
<tr>
<td>30, D.D.</td>
<td>8</td>
<td>M</td>
<td>Lymph.</td>
<td>A</td>
<td>55,000</td>
<td>Low</td>
<td>Aminopterin</td>
<td>9 mgm—9 days</td>
<td>16 days</td>
<td>Still present</td>
<td>No definite</td>
<td>Initial remission still present</td>
<td>5 transfusions 11-11 to 11-13</td>
<td>Living—6½ months</td>
</tr>
<tr>
<td>32, J.S.</td>
<td>45</td>
<td>F</td>
<td>Myel. blast crisis of chr. myel</td>
<td>A</td>
<td>103,000</td>
<td>35,000</td>
<td>A-ninopterin Aminopterin</td>
<td>67.5 mgm—18 days 18 mgm—11 days</td>
<td>49 days (20 d. not incl. phlebitis)</td>
<td>? possible return to chr. state</td>
<td></td>
<td>Transf. p.r.n. Antibiotics</td>
<td>Deceased—4 months</td>
<td></td>
</tr>
<tr>
<td>39, R.G.</td>
<td>3</td>
<td>M</td>
<td>Lymph.</td>
<td>S</td>
<td>34,000</td>
<td>59,000</td>
<td>Aminopterin</td>
<td>7 mgm—7 days</td>
<td>21 days</td>
<td>Still present</td>
<td>No definite</td>
<td>Initial remission still present</td>
<td>Transfusions antibiotics</td>
<td>Living—4 months</td>
</tr>
</tbody>
</table>
or the white cell count had become stabilized at a low level, the drug was resumed in a maintenance dose either parenterally or orally. Maintenance therapy was continued constantly except when a reaction took place. If a relapse occurred, the therapeutic pattern was repeated: increasing the dosage of drug, awaiting a reaction, then returning to the use of maintenance therapy. As most patients experienced at least a mild toxic reaction, they did not feel subjectively improved until subsidence of the reaction. Objective clinical improvement, such as regression of lymphadenopathy and of hepato-splenomegaly, was often noted within a few days after the beginning of treatment. Since an effective dose usually resulted in a "toxic" reaction, it is probable that a therapeutic dose may require the appearance of so-called toxic symptoms.

**Fig. 1b.—Folic acid antagonists**

**Analysis of Cases and Results**

**Analysis of Cases.**

(See tables 1 and 2, and figures 2, 3, 4, 5).

1. *Changes in Subjective Phenomena.* When first seen most of the patients complained of generalized malaise, weakness, weight loss, fever, pallor and such hem-
orrhagic phenomena as epistaxis, bleeding from the gums, menorrhagia, ecchymoses and petechiae. A few complained only of weakness. When a reaction to therapy occurred, the patient usually felt much worse than previously, complaining in addition of various symptoms of toxicity as described below.

After subsidence of the reaction, the patient usually felt improved. If a remission did not occur, the initial symptoms became progressively worse, with death finally supervening, due usually to cerebral or massive gastro-intestinal hemorrhage. If a remission took place, the patient felt much improved and even completely well, the initial symptoms recurring only with another relapse.

2. Objective Phenomena. Most patients showed initially hepatosplenomegaly, lymphadenopathy, marked pallor, petechiae and ecchymoses; in a few, only pallor was present. Following treatment, regression of hepatosplenomegaly and lymphadenopathy occurred, in some particularly sensitive patients within two to three days, in others, at longer intervals. Some patients showed no response what-
soever. The type of reaction was variable from case to case (see below under "Toxic Effects.")

After subsidence of the reaction, and especially when a remission occurred, the patient appeared markedly improved. Physical examination showed no evidence of disease. If a remission did not occur, the patient usually appeared somewhat improved but the leukemic signs became increasingly prominent.

![Graph](https://via.placeholder.com/150)

Fig. 3.—Case 7. (E. W.). Male, age 45. Subacute (leukopenic) lymphocytic leukemia. Note terminal rise in WBC during relapse after remission.

3. Toxic Effects. Reactions usually appeared between five days to three weeks after the initiation of therapy, particularly with aminopterin administration. The first symptoms of reactions were sore mouth and throat, anorexia and nausea; less frequently, vomiting and epigastric discomfort occurred. Stomatitis and pharyngeal injection, especially of the peri-tonsillar pillars, were usually seen at this time together with occasional glossitis. The reaction was usually progressive during the next several days when actual ulcerations of the buccal mucosa and petechiae of the palate could be noted (see fig. 6). Diarrhea with or without gastro-
Fig. 4.—Case 17 (K. B.). Female, age 29. Subacute lymphocytic leukemia. Remission terminated by Torula meningitis. Note rapid marked drop in WBC after onset of therapy.

Fig. 5.—Case 32. (J. S.). Female, age 45. "Myeloblast crisis" of chronic myelocytic leukemia. Note remission and increased duration of usual course.
Fig. 6.—Toxic reactions of oral mucous membrane. (a) (top) Redness and ulceration of buccal mucosa. (b) (bottom) Palatal lesions.
intestinal hemorrhages occasionally occurred. In one case (case 7), right lower abdominal pain came on regularly with administration of the drug. A hemorrhagic skin rash and an apparent aggravation of the bleeding tendency often occurred (see fig. 7). The toxic manifestations might be so severe as to result in death as by massive gastro-intestinal hemorrhage. The severity of the reaction usually depended upon the amount of drug given but even more important was the amount of drug given after the first symptom or sign of a reaction occurred. The effect of the drug appeared to be a prolonged one or cumulative in that even upon withdrawal there was usually a further progression of the reaction for several days. During this period of reaction the patient usually appeared very ill, and at times even semicomatose.

In the early stages of the study, crude and concentrated liver extract, and folic acid were used in an attempt to relieve the toxic symptoms, but were found to be of no definite value. It therefore became our practice simply to discontinue the drug upon the first indication of any symptom or sign of toxicity. This maneuver appeared to be the only therapy of definite value. The reaction usually lasted
for four to seven days, occasionally longer, the duration depending upon the dosage given before the reaction occurred. The margin of safety between a severe toxic reaction and death was at times very small.

Alopecia of varying degree was noted in patients who had been taking the drug regularly for one to two months (fig. 8). This was particularly true in the male patients, many of whom noted a greatly diminished need for hair cuts and shaves. Even with continuation of maintenance therapy, however, regrowth of hair usually occurred within one to two months. A generalized brownish pig-

![Fig. 8.—Alopecia developing during course of folic acid antagonist therapy. Regrowth of hair may occur even though drug is continued.](image)

mentation of the skin usually appeared after the patient had been taking the drug for several months. This pigmentation persisted even though the drug was discontinued.

4. Blood Picture. (a) Peripheral Blood (fig. 9): The peripheral blood usually showed changes within a few days after treatment was instituted, occasionally within several hours. The leukocyte count often dropped very rapidly from high to low levels within two to three days (cf. Case 17, where it dropped from 365,000 to 18,000 within three days' time). If the white count was initially low it usually decreased even further, but the drop was by no means as rapid and spectacular. The primitive cells usually persisted. With remission, the primitive cells began to disappear and mature granulocytes appeared. Finally, an entirely normal dif-
FOLIC ACID ANTAGONISTS IN LEUKEMIA

Fig. 9.—Response on part of peripheral blood (Case 17, K. P.) to folic acid antagonist therapy (X 400).

(a) Before treatment, July 16, 1948. WBC 315,000. Almost all lymphoblasts.
(b) Period of reaction, August 1, 1948 (7 days). Few leukocytes, still no platelets.
(c) Beginning remission, August 13, 1948 (18 days). WBC 4,000. Marked increase in platelets; reappearance of granulocytes.
(d) Complete remission, September 20, 1948 (56 days). WBC 8,000. Normal differential and platelets.
ferential count often developed. During the period of remission this normal leuko-
cytic picture persisted, although occasional primitive cells appeared at times in
the peripheral blood.

The red cell count did not improve spontaneously until remission occurred after
subsidence of the initial reaction. During continued remission the red cell count
increased or maintained itself without further transfusions. Reticulocytes often
became increased at the beginning of the remission.

The platelets were almost constantly decreased initially. At times they rose as
the initial indication of a remission but usually they were the last elements in
the blood to respond to therapy. If a complete remission ensued, the platelets
became increased approximately twenty to thirty days after the beginning of
treatment. In some instances, the other elements in the peripheral blood showed
well defined indications of remission although the platelets might fail to rise.
This usually indicated an incomplete remission and the probability of quick re-

(b) Bone Marrow (fig. 10): Changes in the bone marrow could usually be cor-
related with those in the peripheral blood. Within one to three weeks after in-
stitution of treatment, the marrow became hypoplastic and there appeared to be
fragmentation of primitive cells. In the favorable cases, recovery of the marrow
usually occurred during or shortly after the period of recovery from the toxic re-
action, following which a normal type of granulocytopenesis returned with a
practically normal type of orderly maturation. A certain number of abnormal
primitive cells was almost always noted even during complete remission.

During the phase of recovery from the hypoplastic phase, erythropoietic ele-
ments also appeared and showed an orderly type of normoblastic maturation.
Occasionally a few cells resembling megaloblasts appeared in the marrow after
several weeks or months of therapy. During the period of continued remission,
normal erythropoiesis persisted.

Megakaryocytes were not usually seen in the marrow in treated cases. If a re-
mission occurred, they appeared at the time of recovery from the hypoplastic
phase and shortly thereafter increased number of platelets appeared in the periph-
eral blood. The appearance of megakaryocytes was usually an excellent indication
for the presence of a well-defined remission.

The hematologic indications of a remission were the development of a normal
white count and differential and platelet count, a marked reduction of primitive
cells in the marrow, either an increase or maintenance of the red cell count in the
peripheral blood without transfusion and an appearance of megakaryocytes and
erthroblastic islands in the marrow. During the period of complete remission
the diagnosis of leukemia could be made only with difficulty. When a relapse
occurred, the marrow and peripheral blood reverted to the typical picture of acute
or subacute leukemia as seen before institution of therapy.

5. Hemorrhage. The immediate cause of death in most of the cases in this series
was hemorrhage, which was usually associated with a marked thrombocytopenia.
The possibility of an increase in heparin or heparin-like substance was considered,
but the administration of toluidine blue and protamine were of no value. Trans-
Fusions of fresh blood, preferably from patients with high platelet levels, appeared to be the only good method for improving the hemorrhagic state. In occasional cases having reactions to whole blood, washed red cell transfusions were given.
6. **Auxiliary Treatment.** All our patients received transfusions and antibiotics as indicated and there can be no doubt that this additional therapy played an important role in contributing to the remissions obtained. However, the primary cause for the clinical and hematologic effects observed must be ascribed to the use of the folic acid antagonists. Close study of our data indicates that the use of frequent transfusions during the period of toxic reaction or after the initial effect was obtained was of some help in the ultimate recovery from the hypoplastic state of the marrow induced by the initial chemotherapy. Fresh whole blood or washed red cell transfusions were always used. Penicillin, streptomycin or sulfadiazine were given as indicated. In any case with a leukocyte count of 1000 or less, penicillin was given prophylactically. In only 2 of our cases did infection appear to play a prominent role in causing death. One patient (Case 17) died of Torula encephalo-meningitis, first manifested during a period of complete remission; and another (Case 3) died with a large pulmonary abscess. Both of these patients had previously received large doses of the various antibiotics.

Adequate oral hygienic care, especially during the phase of reactions, was found to be of importance. There is no need to mention the necessity and beneficial effects of adequate nursing and psychologic care particularly during the period of severe reaction. At times the patient undoubtedly felt that the treatment was worse than the disease, and during this time everything possible was done to relieve symptoms and to bolster the patient’s courage.

**Analysis of Results**

We classified our cases into acute and subacute types. This division is to a large extent arbitrary, depending upon the duration of symptoms before treatment was instituted, their severity when first seen, the blood picture and platelet count and hemorrhagic tendency. A far higher incidence of remissions occurred in the relatively slowly developing or subacute cases. The least favorable results were obtained in the fulminating cases. Of the 40 cases, 6 were under 15 years of age; of these, 5 received an adequate trial of therapy. Three showed remission. Comparable results occurred in both "leukemic" and "aleukemic" cases, and in fact some of our best and most sustained results were obtained in the aleukemic types.

1. **Remission Rates** (table 2). Of 32 cases given an adequate therapeutic trial, 10 developed a remission lasting for at least two months and continuing more or less intermittently up to thirteen months (as of June 1, 1949). A remission was considered to be present when the patient (a) felt subjectively improved; (b) showed such objective clinical improvement as remission of lymphadenopathy and hepato-splenomegaly and loss of hemorrhagic tendency; (c) showed hematologic improvement as evidenced by increase in the red cell count, return of leukocyte and differential counts to relatively normal values; a definite increase in blood platelets if low, and an improvement in the marrow picture; and (d) showed continuous improvement for at least two months.

The remission rates were as follows: Overall results: 40 cases (8 dying within one week’s time): 10 remissions (25.0 per cent). Adjusted results: 32 cases (treated over one week’s time): 10 remissions (31.3 per cent).
2. Types of Cases Treated (table 2). We have further analyzed our cases and remissions with respect to the type of proliferating cell involved. Admittedly, this may be a difficult procedure. By the use of the ordinary Romanowsky stains, together with oxidase stains, supravital staining and phase microscopy, and some histochemical methods including particularly the use of sudan black, we were able to classify the type of leukemia in 36 of the 40 cases.

Our best therapeutic results were obtained in the lymphocytic cases: none of the four cases of monocytic leukemia responded:

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases</th>
<th>Remissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Granulocytic (Myelocytic)</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Monocytic</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Unclassified</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Discussion

In the evaluation of any new therapy for a disease one must know the natural history of the disease without therapy as well as its course when other therapeutic agents are used. At a conference on folic acid antagonists held in Boston in January 1949, several hematologists gave their impressions regarding the occurrence of spontaneous remissions in acute leukemia. Diamond stated that of 300 children with acute leukemia, about 10 per cent experienced either complete or partial spontaneous remissions, and in almost 75 per cent of these there was a history of antecedent infection. These remissions averaged slightly less than ten weeks in duration. Zuelzer stated that almost 10 per cent of 60 children experienced spontaneous remissions, which were almost totally confined to those with peripheral leukopenia. Poncher emphasized, however, that the bone marrow in these remissions seldom showed any signs of any improvement. Dameshek reported that the spontaneous remissions in adults were very rare, occurring in 1 to 2 per cent or less of his cases. Ross stated that he had never observed a spontaneous remission in an adult. Rosenthal reported that of approximately 2000 cases he had observed,
only six spontaneous remissions occurred, with one patient experiencing two of these two months apart. Of these, only two showed bone marrow improvement. He felt that transfusions were probably the important factor in bringing about the spontaneous remission in these few cases. Bessis used complete exchange transfusions in the treatment of acute leukemia: of 38 cases treated he reported complete remissions in 6 and incomplete in 15.

It is evident from these data that therapy with folic acid antagonists resulted in a much higher remission rate in acute leukemia than would be expected from the natural history of the disease or experienced with other forms of therapy. It must be conceded that the remissions were of a temporary nature; certainly one cannot speak of "cures" with the medication. The duration of a remission was extremely variable (see table of remissions). Although maintenance therapy was given, a relapse usually occurred which might not respond to increased dosage. One of the cases (Case 1) experienced two remissions, finally succumbing to a third relapse eight and one-half months following institution of therapy. Another (Case 32) showed a tendency to relapse within two to three days after each omission of the drug, with the white count rising rapidly and the spleen becoming enlarged. These manifestations disappeared almost as quickly when the drug was given again. The longest remission in this series was thirteen months (as of June 1, 1949) after onset of therapy, with the patient still alive and in good health.* In the great majority of cases, there finally came a point in the leukemic process at which both the leukemia and toxicity to increasing the dosage of the drug made further progress impossible, following which the patient died.

At the above-mentioned conference on folic acid antagonists, considerable variation in results obtained was reported by different investigators. Some observed practically no beneficial effects in any case, whereas others felt quite encouraged by the use of these drugs. Farber reported the largest series of cases, all in children, with remissions occurring in approximately 68 per cent of 9 patients treated over three weeks, the remissions being complete in 37.5 per cent of the cases.12 Our cases, mostly adults, appeared to show the best remission rate in the reported cases in adults. It is possible that this variation in results is explained not only by the natural variability of acute leukemia from case to case but by varying considerations as to what is constituted by a remission. Such factors as different methods of dosage patterns and the type of maintenance therapy employed by the various groups of workers might also be of distinct importance.

It appears that the folic acid antagonists, although by no means curative in acute leukemia, offer the first ray of hope in the treatment of this disease and may be the precursors of more effective and less toxic drugs. Thus, the results of therapy may be said to represent the beginning of a new era in the therapy of this dread disease. They also lend support to the thesis that in chemotherapy may lie the fate of the ultimate control of cancer and related diseases.

* This patient continued in good health until May 1950 when he had another relapse. This was treated with transfusions and larger doses of aminopterin and again the patient had a remission which has now (June 1, 1950) lasted altogether twenty-five months.
Summary

Forty cases of acute and subacute leukemia were treated with one or more of various folic acid antagonists, usually aminopterin. Thirty-two cases were treated for at least one week, remissions occurring in 10. The remissions were of a temporary nature and variable in duration. As of June 1, 1949, two patients were still alive and in good condition, seven and one-half and thirteen months, respectively, after onset of therapy.

Clinical, hematologic, and to lesser extent, marrow remissions were obtained most commonly in the lymphocytic type, none in the 4 monocytic cases. The subacute cases responded far better than did those of the acute, fulminating variety.

The exact mechanism of action of the folic acid antagonists is not known, although one may speculate that anti-PGA, an anti-growth factor which resembles PGA so closely, is readily accepted by the primitive white cell with resultant cell death.

The margin between a therapeutic or effective dose and one causing a toxic reaction is a narrow one. A "toxic" reaction may in fact be an indication of a therapeutic response.

The pattern of therapy was (1) administration of the drug, usually by parenteral injection until a toxic or a pronounced hematologic reaction occurred, at which point (2) the drug was discontinued. With subsidence of the toxic reaction, (3) a maintenance dosage was then given, usually in the form of oral medications, 0.5 mg. daily for adults and 0.25 mg. for children.

Transfusions and antibiotics were administered as indicated. Frequent transfusions were usually very helpful at the time of the initial reaction when anemia was ordinarily severe. Penicillin and other antibiotics were used for supportive therapy. Thrombocytopenia and hemorrhage were exceedingly difficult to control.

The observed remissions appeared to be directly attributable to the action of the drug. Although temporary, they indicate that acute leukemia is not necessarily completely irreversible. Thus, there is hope that more potent anti-growth factors may someday be discovered which will be of value in ultimate control of the disease.

Addendum

Of the 5 patients reported in table 1 as having remissions still present at the time the manuscript was written (June 1949), only 2 were alive in June 1950. The first one, E. D. (Case 6) has shown by far the best results of the series and responds regularly and remarkably to the drug. He is now in a state of excellent remission 25 months after therapy was first initiated.

The second, R. G. (Case 39), had three excellent remissions, lasting altogether eleven months, but in his third relapse there was no further response to aminopterin. Upon admission to the hospital in March 1950 his marrow showed complete replacement with leukemic cells and his condition seemed desperate. He was treated with ACTH (Bull. New England M. Ctr. 12: 11-21, February, 1950) and began to show reticulocyte and platelet responses in three and one-half weeks.
He then went on to an almost complete remission lasting for eight weeks. Relapse then occurred while the patient was under maintenance cortisone therapy. Another minor remission was induced by persistent ACTH therapy but at the expense of the typical so-called side effects of the continued use of this hormone.

ACKNOWLEDGMENTS

We are pleased to acknowledge the continued cooperation and generosity of various members of the Staff of Lederle Laboratories. We wish particularly to mention the help of the late Doctor Yellapragada SubbaRow, who was greatly interested in some of our first remissions obtained in adults. We also wish to thank the staffs of the U. S. Veterans Hospital at West Roxbury (Dr. Thomas Warthin, Physician-in-Chief) and of the Murphy General Hospital for their cooperation. We are greatly indebted to the medical and nursing staffs of the Boston Floating Hospital (Dr. James H. Bay, Physician-in-Chief) and of the New England Center Hospital (Dr. Samuel Proger, Physician-in-Chief).

REFERENCES

12 Conference on Folic Acid Antagonists at Children's Hospital, Boston, Massachusetts. January 9, 1949.
FOLIC ACID ANTAGONISTS IN THE TREATMENT OF ACUTE AND SUBACUTE LEUKEMIA

WILLIAM DAMESHEK, MILTON H. FREEDMAN and LESTER STEINBERG