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TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

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IT IS the purpose of this paper to record the results of clinical and hematologic studies on 5 children with acute leukemia treated by the intramuscular injection of a synthetic compound, 4-aminopteroylglutamic acid (aminopterin). This substance is an antagonist to folic acid regarding the growth of *Streptococcus faecalis R.*

The occurrence of what he interpreted as an "acceleration phenomenon" in the leukemic process as seen in the marrow and viscera of children with acute leukemia treated by the injection of folic acid conjugates[1] — pteroyltriglutamic acid (teropterin) and pteroyldiglutamic acid (diopterin) — and an experience gained from studies on folic acid deficiency suggested to Farber that folic acid antagonists might be of value in the treatment of patients with acute leukemia.[2] Post-mortem studies of leukemic infiltrates of the bone marrow and viscera in patients treated with folic acid conjugates were regarded by Farber as evidences of an acceleration of the leukemic processes to a degree not encountered in his experience with some 200 post-mortem examinations on children with acute leukemia not so treated. It appeared worth while, therefore, to ascertain if this acceleration phenomenon could be employed to advantage either by radiation or nitrogen mustard therapy after pretreatment with folic acid conjugates or by the administration of antagonists to folic acid.[2] A series of folic acid antagonists was made available by Dr. Y. Subbarow and his colleagues.[3–5]

The objective data sufficient to justify research in the direction of antagonists to folic acid in the treatment of leukemia were obtained from studies on a four-year-old girl with a rapidly progressing acute myelogenous leukemia.[2] Treatment from February 17 to March 24, 1947, with pteroyldiglutamic acid (diopterin), in a dosage of 100 to 300 mg. intramuscularly daily, had no effect upon the hematologic picture. The patient appeared to be moribund. A second bone-marrow biopsy on March 25 verified the diagnosis of myelogenous leukemia. Pteroylaspartic acid, the first antagonist to folic acid to be employed in our studies, was given intramuscularly from March 28 to April 4 in amounts of 40 mg. daily without altering the clinical course. Post-mortem examination on April 4 revealed a markedly hypoplastic bone marrow, with a few immature cells. A change of this magnitude in such a short time has not been encountered in the marrow of leukemic children in our experience.

This observation was followed by clinical, laboratory, and post-mortem studies** on a group of 14 children with acute leukemia treated with pteroylaspartic acid and on 7 treated with methylpteroic acid. The details of these observations will be reported separately.

Sufficient encouragement was obtained from these observations to justify further studies on the effect of more powerful antagonists to folic acid on the course of acute leukemia in children. Since November, 1947, when a sufficiently pure substance became available, to the time of this writing (April 15, 1948) we have made studies on 16 children with acute leukemia to whom the most powerful folic antagonist we have yet encountered, 4-aminopteroylglutamic acid (aminopterin††) was administered by intramuscular injection. Many of these children were moribund at the onset of therapy. Of 16 infants and children with acute leukemia treated with aminopterin 10 showed clinical, hematologic and pathological evidences of improvement of important

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**These studies were carried out by a group consisting of Sidney Farber, Gilbert G. Lenz, James W. Hawkins, Ernst Eichwald, Robert D. Mercer and E. Converse Peirce, II.

††This compound was first synthesized by the Calco Chemical Division of the American Cyanamid Company.

nature of three months' duration at the time of this report. Six patients did not respond well; 4 of these are now dead, and 2 were unimproved. This paper presents detailed clinical, hematologic and bone-marrow studies in 5 children selected from these 10 who showed evidences of important improvement — the course in the other cases was essentially similar. The patients are selected for the purpose of illustrating some of the problems concerned with the use of aminopterin and because they demonstrate the best results that we have

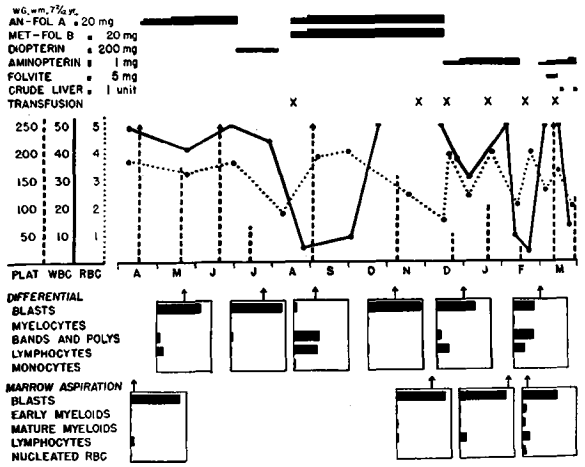

FIGURE 1. *Course of Leukemia in Case 1.*

observed. The toxic effects are stressed in these histories, and the temporary nature of the remissions is emphasized.

CASE REPORTS

CASE 1. W. G., a 7 2/12-year-old boy, entered the hospital for the first time on April 9, 1947, with complaints of joint pain and fever. He had been generally well until 7 weeks before admission, when pain developed in the right knee. There were no associated physical abnormalities, and the pain promptly subsided. Five days later pain recurred in the right elbow, and a low-grade fever was noted. Migratory arthralgia and fever continued until admission.

Physical examination revealed only moderate pallor and slight enlargement of the liver and spleen. The boy appeared well developed and nourished and not particularly ill.

Examination of the blood disclosed a red-cell count of 3,670,000, with a hemoglobin of 10.6 gm., and a white-cell count of 56,000, with 73 per cent blast forms. The platelet count was normal. A bone-marrow biopsy revealed leukemia.

The patient was treated with pteroylaspartic acid beginning on April 16 in doses of 20 to 60 mg. daily while in the hospital, in a convalescent home, where he remained until May 20, and at home, where the injections were given by the family physician. During that time he was active and fairly well, although the white-cell count remained high and the red-cell count and hemoglobin fell slowly.

On July 1 diopterin, in a dosage of 200 mg. by mouth daily, was begun. This therapy was continued for about 1 month, during which the patient steadily became more ill. The liver and spleen enlarged, and he became very anemic. The blast forms in the peripheral blood rose to 94 per cent. Joint pain and fever recurred, and by August 13 he was critically ill, with a temperature reaching 106°F. He was readmitted to the hospital and received several transfusions. Pteroylaspartic acid and methylpteroic acid, in doses of 40 mg. each, were given intramuscularly daily. The patient was discharged after about 2 weeks, and pteroylaspartic acid and methylpteroic acid, in doses of 20 mg. each, were continued in the Tumor Therapy Office. A period of remission ensued, during which the red-cell count and platelets returned to normal levels, the liver and spleen receded in size and the nutrition improved remarkably. He returned to school part time in October and was in quite good condition. The white-cell count had risen to high levels, however, and in November general deterioration began. The liver and spleen enlarged, and he became so anemic that transfusion was necessary by November 24. Only temporary benefit resulted and transfusions were required at about 3-week intervals.

Aminopterin was started on December 16 and given daily, in doses of 0.5 mg. intramuscularly, for six doses. By December 30 the white-cell count had fallen from 60,000 to 19,000. There was moderate improvement in activity and appetite. Thereafter unfavorable weather made daily visits to the clinic impossible, and 1 mg. of aminopterin was given approximately three times weekly for about a month. During that time there was no striking clinical or hematologic improvement, although the patient was not seriously ill.

On February 3 daily injections of 1 mg. of aminopterin were begun. A bone-marrow biopsy and aspiration revealed 85 per cent blast forms, no megakaryocytes and no erythropoiesis. After 10 days of regular therapy the white-cell count had fallen from 78,000 to 5000, but severe stomatitis made cessation of therapy imperative. Within a week without therapy, the stomatitis had healed completely, and the patient had developed a ravenous appetite. The nutrition gradually improved. By February 21 the liver was no longer palpable, and only the tip of the spleen could be felt. Bone-marrow aspiration and biopsy revealed a slight decrease in blast forms and slight erythropoietic activity. The platelets reached normal levels about 1 month after this course of daily therapy. On March 1 the white-cell count began to rise in spite of daily administration of 0.25 mg. of aminopterin, and by March 6 was 75,000. The spleen again enlarged. The dosage of aminopterin was raised to 1 mg. on March 8, and after about 10 days the white-cell count had fallen to 12,000. Slight stomatitis again appeared, and the dosage of aminopterin was reduced to 0.5 mg. daily, with 1 unit of crude liver extract weekly. The white-cell count has remained at a high-normal level, and the spleen is again slowly receding. The stomatitis is still present but is not progressing and does not interfere with ability to eat.

The leukemia in this case progressed slowly during treatment with pteroylaspartic acid and methylpteroic acid, but during a course of diopterin became rapidly worse (Fig. 1). The liver and spleen enlarged, severe anemia developed, and the blast forms in the peripheral blood rose above 90 per cent. The patient appeared critically ill, with a maximum temperature of 106°F. Transfusions and therapy with these two folic acid antagonists were followed by a marked but temporary remission. Irregular therapy with aminopterin has been of no benefit, but on two occasions daily injections have produced good clinical and hematologic remissions. On both occasions, stomatitis has interfered with optimal use of the drug. At the time of writing the patient is in excellent physical condition.

CASE 2. R. P., a 6 4/12-year-old boy, was admitted to the hospital on March 4, 1948, with the chief complaint of increasing pallor. His growth, development and general health had been excellent until about 3 weeks before admission, when tonsillitis had developed. This had subsided promptly, but the patient had become lethargic, and increasing pallor was noted. About 10 days before admission his parents began to notice that he bruised easily.

Physical examination disclosed a well developed and fairly well nourished boy who was very pale and lethargic. Many small ecchymoses were noted over the extremities. The liver edge extended 4 cm. below the costal margin, and the tip of the spleen could be felt at the costal margin. There was slight generalized lymphadenopathy.

Examination of the blood revealed a red-cell count of 1,880,000, with a hemoglobin of 5.65 gm. and platelets of 46,000, and a white-cell count of 4200, with 20 per cent immature or blast forms. A sternal-marrow aspiration revealed 75 per cent blast forms. No megakaryocytes were seen.

Shortly after admission the patient developed a spiking temperature up to 104 or 105°F. daily, and rapidly became more lethargic. Blood cultures revealed no growth. Frequent transfusions raised the red-cell count and hemoglobin to normal levels, but there was no favorable clinical response. The white-cell count fell to 1500. He appeared critically ill. On the 7th hospital day penicillin was started, and the temperature decreased although it continued to reach 101 to 102°F. daily.

On the 8th hospital day, aminopterin (1 mg.) and crude liver extract (1 unit) were given intramuscularly. The white-cell count was 1500. This medication was continued daily, and the patient rapidly became more alert and active. The white-cell count remained near 2000. He was discharged moderately improved on March 15. After discharge he was seen 6 times weekly in the Tumor Therapy Clinic and 1 mg. of aminopterin and 1 unit of crude liver extract were given at each visit. Rapid improvement in appetite and activity continued. A second sternal-marrow biopsy and aspiration after one week of therapy revealed a 25 per cent decrease in blast forms and an increase in more mature leukocytes and megakaryocytes. By March 25 the white-cell count had reached 5000, with 34 per cent neutrophils, 63 per cent lymphocytes and 2 per cent blast forms. His activity and appetite were normal and easy bruising was no longer a complaint. At about that time he developed minor

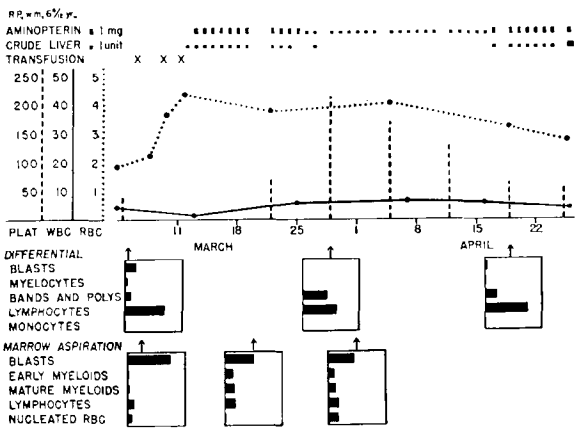

FIGURE 2. *Course of Leukemia in Case 2.*

lesions of the oral mucosa. The dosage of aminopterin was reduced to 0.5 mg., and the liver extract was given once weekly. Steady improvement has continued. The liver and spleen are no longer palpable. The patient is active in outdoor games, and his endurance is good. On March 31 he returned to school, where his teacher noted marked improvement in his appearance and interest. Sternal-marrow aspiration on April 1 revealed a slight further reduction in blast forms, a moderate increase in megakaryocytes and a marked increase in erythropoiesis. He continues on daily injections of 0.5 mg. of aminopterin with liver extract once weekly.

This patient had rapid progression of leukemia until one month after the onset, when he appeared critically ill. After three weeks of daily aminopterin therapy his activity and appearance have returned to normal and he is in school part time. The red-cell count and hemoglobin are still high, and the white-cell count is within normal limits. Immature cells or blast forms have disappeared from the peripheral blood, and the bone marrow shows a moderate shift toward maturity of leukocytes, with an increase of erythrocyte precursors and megakaryocytes. The course is demonstrated in Figure 2.

CASE 3. G.J., a 3 8/12-year-old boy, was admitted to the hospital on November 2, 1947 — 5 days after the onset of an acute illness with sore throat and fever.

The past history, birth and developmental history were not remarkable.

Physical examination disclosed a critically ill patient with an acute follicular tonsillitis and enlarged tender cer-

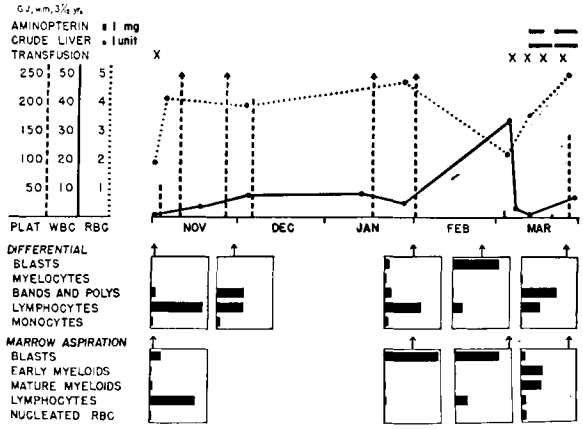

FIGURE 3. *Course of Leukemia in Case 3.*

vical lymph nodes. There was no generalized adenopathy and no hepatomegaly or splenomegaly. A blood culture was positive for beta-hemolytic streptococcus.

Examination of the peripheral blood showed a red-cell count of 1,900,000, a white-cell count of 480 and a platelet count of 123,000. Bone-marrow aspiration showed 16.4 per cent blast forms, 3.2 per cent mature polymorphonuclear leukocytes, 76.2 per cent lymphocytes and 1.6 per cent erythroid elements. On the basis of the bone-marrow aspiration a diagnosis of leukemia was made. The bacteremia was treated with penicillin and streptomycin.

After recovery from the infection the patient went into a complete clinical and hematologic remission for about 2 months. The course is demonstrated in Figure 3. At that time bilateral acute otitis media developed. Two weeks later the total nucleated count of the sternal bone marrow was 910,000 (normal 200,000 to 250,000), with 96 per cent blast forms (Fig. 4*A*). By February 26, 1948, the white-cell count was 17,250, with 80 per cent blast forms, the spleen extended to the umbilicus, petechiae began to appear, and it was obvious that the child was entering a rapidly progressive phase of the leukemia.

He was readmitted to the hospital on March 6. He appeared chronically ill, with pallor, petechiae, moderate generalized lymphadenopathy and marked hepatomegaly and splenomegaly. The white-cell count, which was 30,400, with 86 per cent blast forms, on admission, fell rapidly to 900 by March 12, and the patient appeared moribund. Blood cultures were negative.

Aminopterin was started on March 13 in doses of 0.5 mg. and given for 5 consecutive days. Crude liver extract, in a dosage of 1 unit daily, was given in the same syringe. At

the end of that time there was no noticeable clinical improvement, but the white-cell count, which was still 900, contained only 5 per cent blast forms. A sternal-marrow smear made at the end of this short period of therapy and compared to one just before therapy was started showed a shift to the right, with some reduction in blast forms and an increase in more mature forms of granulocytes, as well as a slight increase in erythroid elements. Aminopterin was discontinued until it became apparent that the leukopenia was not increasing.

After 4 days without treatment 0.5 mg. of aminopterin daily, with 1 unit of crude liver extract, was given once more. The white-cell count increased gradually, and blast forms disappeared from the peripheral blood. The child began to show clinical improvement, his appetite became better, and the liver and spleen became scarcely palpable. The petechiae and generalized adenopathy disappeared.

At the present writing there is a partial contracture of the left leg, probably resulting from leukemic infiltrations about the knee joint and in the gastrocnemius muscle. The tip of the spleen is still palpable. Otherwise the child is normal on physical examination. The white-cell count is 6700, with a normal differential. The platelet count is 152,000. Aspiration of the sternal marrow on March 29 revealed 8 per cent blast forms, with an increase in more mature granulocytes, erythrocyte precursors and megakaryocytes (Fig. 4*B*).

This child with acute leukemia had a remission of about two months' duration after a bacteremia. At the time aminopterin was started he was in a rapidly progressive phase of the leukemia and appeared moribund. After five days of therapy there was marked improvement in the peripheral-blood and sternal-marrow picture. He has continued to demonstrate rapid and remarkable clinical improvement. Eighteen days after therapy was started the sternal-marrow aspiration showed only a slight shift toward immaturity of the myeloid elements and a moderate reduction of lymphocytes and erythroid elements. The peripheral blood at present shows slight thrombocytopenia, with a white-cell count of 8000 and a differential count that is essentially normal except for a large number of band forms.

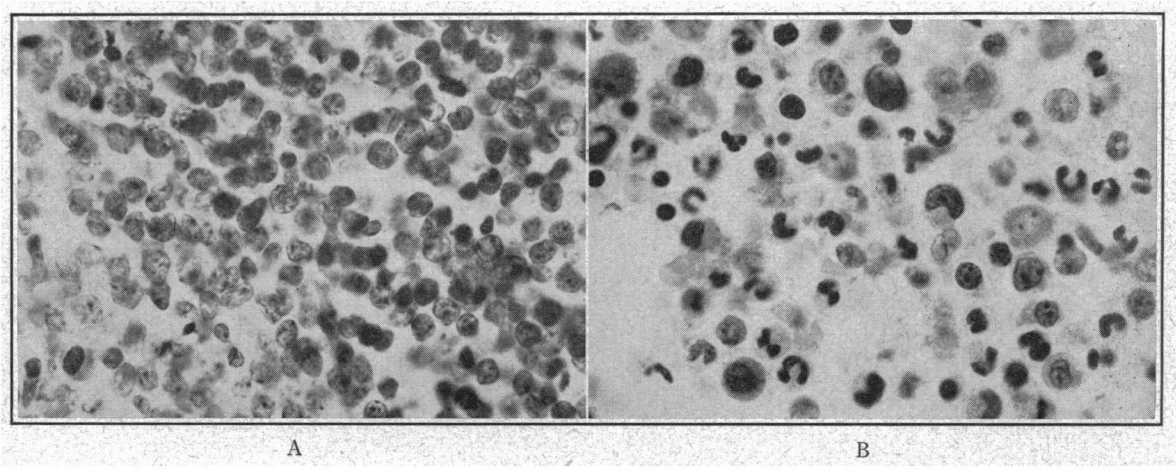

FIGURE 4. *Photomicrographs of the Sternal Bone Marrow in Case 3, Showing Giemsa-Stained Section on January 29,* (A) *and April 3* (B), *1948* (*x1000*).

Note that the microscopical field is composed mainly of blast forms characteristic of leukemia (cell type undetermined) in the early section (A) *and that a marked shift to mature cell forms, particularly of the polymorphonuclear series, with no leukemic cells, had occurred on the later examination* (B).

CASE 4. C. C., a 2 1/12-year-old girl, was admitted to the hospital on August 22, 1947. Six weeks previously her father had noticed lumps about the head and neck. Two weeks previously her family physician had made a diagnosis of leukemia on the basis of a peripheral blood smear.

Physical examination revealed a pale girl, with ecchymotic areas over the lower extremities. There was marked generalized adenopathy, particularly about the parotid region, and the liver edge and tip of the spleen extended down to the iliac crests.

Examination of the blood disclosed a white-cell count of 75,000, with 80 per cent blast forms. The platelet count was 54,000. The patient was discharged and given x-ray therapy to the parotid region in the outpatient department. A total of 600 r was given from September 4 to September 8. The white-cell count, which was 94,000 on September 4, had dropped to 5000 by September 11.

The patient was readmitted on September 27. She was much worse, with a poor appetite, marked pallor and massive adenopathy. The white-cell count was 1000, with 30 per cent blast forms. Several transfusions before discharge produced only slight improvement.

The third admission, on November 6, followed a generalized convulsion. The patient was comatose, with a temperature of 103.6°F.

Physical examination was essentially unchanged except that the kidneys were definitely enlarged and easily palpable. There was no positive evidence of infection. A transfusion and penicillin were given, and the patient was discharged in fair condition.

The fourth and last admission was on December 2, when there was a temperature of 105°F. There was a severe stomatitis and pharyngitis, with extensive exudation. The left ear was inflamed but not suppurating. Bronchopneumonia was present on the left. A lumbar puncture showed evidence of subarachnoid hemorrhage. A blood culture was positive for *Staphylococcus aureus*, coagulase positive.

For the first 6 hospital days the patient ran a septic temperature ranging between 105 and 103°F. She was given penicillin and sulfadiazine, as well as repeated blood transfusions, throughout the hospital stay. At this admission she was seen for the first time by the Tumor Clinic and received 20 mg. of teropterin per day for eighteen doses, from December 3 through December 20.

On several occasions the patient appeared moribund but on about the 7th hospital day she began to improve and continued to improve until the time of her discharge. The white-cell count, which had dropped to 650 on the 4th hospital day, rose to 6400 on the day before discharge. The differential count included 68 per cent neutrophils, 24 per

cent lymphocytes and 8 per cent monocytes. There were no blast forms.

After this severe infection there was a remission in the clinical and hematologic condition. During that time the patient was given an occasional dose of teropterin to a total of 140 mg. By January 13 small lymph nodes over the scalp, parotid and cervical regions had begun to develop. These rapidly increased, and by January 19 there was massive generalized adenopathy. The peripheral blood and bone marrow continued at values approaching normal. There were only occasional to 5 per cent blast forms in the peripheral blood, with a normal total white-cell count, and 8.4 per cent blast forms in the bone marrow, with a slight depression of mature forms and a moderate depression of erythroid forms. On January 20 aminopterin was started in doses of 1 mg. daily with 20 mg. of teropterin daily. This was given on twenty-six clinic visits from January 20 to February 21. Four days after treatment had been started there was a marked decrease in the size of all the lymph nodes. In 2 weeks the patient was normal on physical examination. Her appetite became very good, her disposition happy, and she began to play and run about like a normal child. Her parents stated that she was better than she had been before she became sick for the first time. Since treatment was stopped she has continued to do well. She has been without treatment since February 21 and at present is completely normal on physical examination. The total white-cell count is 9000, with an occasional blast form. The platelet count is 256,000, the red-cell count 4,600,000 and the hemoglobin 14.8 gm.

This child is known to have had acute leukemia since early in August, 1947. Her course was rapidly and progressively downhill until December, when she had a fulminating generalized infection with bacteremia. After this she had clinical and hematologic evidence of remission. In the middle of January a relapse was taking place, as evidenced by massive generalized adenopathy although the blood and bone-marrow picture remained the same. After aminopterin therapy the adenopathy disappeared. The patient has remained clinically well for forty-three days without treatment and shows an essentially normal hematologic picture at the time of writing. The course is shown in Figure 5. At the end of forty-seven days without treatment a few nodules appeared beneath the scalp and in the subcutaneous tissue over the face. It is probable that these represented leukemic deposits, although at the time of their appearance the peripheral blood was still essentially normal. Because of this finding the treatment has been reinstituted.

Case 5. R. S., a 2 2/12-year-old boy, was admitted to the hospital on August 26, 1947, with the chief complaint of increasing pallor. He was one of identical twins, and his birth, growth and development, and general health had been unremarkable. About 10 days before admission he had developed a low-grade fever, soon followed by increasing pallor, lethargy, anorexia and intermittent vomiting.

Physical examination showed a fairly well developed and well nourished and only moderately ill boy. He was very pale. There was generalized enlargement of the lymph nodes and moderate hepatomegaly and splenomegaly. X-ray study showed marked infiltration of the long bones. The hemoglobin was 5.5 gm., and the white-cell count 12,400, with 41 per cent immature or blast forms.

During 2 weeks in the hospital the patient received transfusions, which restored the hemoglobin to normal levels. After discharge he was seen in the Tumor Therapy Clinic daily except Sunday and on each visit received 20 mg. of pteroylaspartic acid intramuscularly. He continued on this regime for about 2 months, during which the disease progressed slowly but steadily. He became less alert and less active. He developed a limp. There was gradual weight loss, and the liver and spleen continued to enlarge. The leukocytes remained at normal levels but the percentage of blast forms increased. The red-cell count and hemoglobin slowly fell, until on November 6 it was necessary to admit him to the hospital for transfusion. At that time a small pathologic fracture was noted in the left tibia. After discharge he was seen in the Tumor Therapy Office three times weekly and on each visit received 40 mg. of pteroylaspartic acid intramuscularly. Late in November there was a definite acceleration in the progress of the disease. The white-cell count began to rise, and the platelets fell. The patient began to bruise easily and had occasional slight oozing from the gums. He developed moderate exophthalmos. He refused to walk. Hospitalization was necessary twice in the

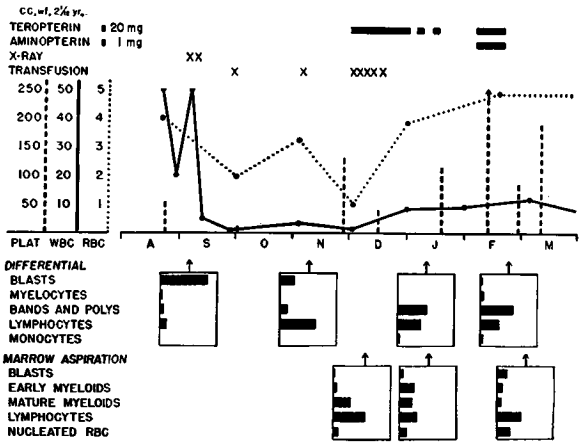

Figure 5. *Course of Leukemia in Case 4.*

early weeks of December for treatment of arthritis and upper respiratory infection. Sternal-marrow aspiration at that time revealed 40 per cent blast forms and little erythropoiesis. By the end of December the patient appeared moribund. He had marked generalized adenopathy, marked hepatomegaly and a spleen whose tip extended into the pelvis. There was moderate dyspnea and stridor, pallor, marked wasting and exophthalmos. There were many ecchymoses, and oozing occurred at the gingival margins.

Aminopterin therapy was begun on December 28. On each of 3 successive days the patient received 1.0 mg. of the drug intramuscularly. During that time the white-cell count began to fall rapidly from the pretreatment level of 60,000. By December 31 the count was 9000, and respiratory difficulty was even more marked. He was admitted to the hospital, aminopterin was discontinued, and a transfusion was given. He was discharged on January 3, 1948, slightly improved, but with the white-cell count only 2700. After discharge he was again followed in the Tumor Therapy Clinic. By January 13 marked clinical improvement had become apparent. The patient was walking for the first time in 2 months, and respiratory difficulty had disappeared. His appetite was ravenous. There was no more bleeding. "His clothes became loose about the abdomen." On January 27 the white-cell count reached 5000, and 0.5 mg. of aminopterin was started and given three times weekly. Gradual improvement continued, but a white-cell count of about 3000 persisted. In the middle of February, teropterin in 10-mg. amounts was given with each dose of aminopterin for five doses. Early in March a rise in the hemoglobin and red-cell count began. Since then folic acid for a time and lately crude liver extract have been used in conjunction with aminopterin. There had been steady clinical and hematologic improvement so that at the time of writing, activity, alertness and nutrition are equal to or better than those of the well twin. The liver and spleen have decreased in size, so that they are barely palpable beneath the costal margins. Exophthalmos has disappeared. The red-cell and white-cell

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