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The treatment of the leukemias with folic acid antagonists

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THE TREATMENT OF THE LEUKEMIAS WITH FOLIC ACID ANTAGONISTS

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HISTORY OF DEVELOPMENT OF FOLIC ACID ANTAGONISTS

Farber and collaborators,(1) during their studies on the leukemias in childhood found that folic acid and related compounds such as diopterin, pteroyldiglutamic acid and pteroyltriglutamic acid, produced a marked hyperlasia of bone marrow and leukemic infiltrations, "acceleration phenomenon." Heinle and Welch(2) noted similar results.

Little(3) in his studies of folic acid deficient states on the growth of neoplastic tissue, found that tumor growth was inhibited in chicken sarcoma.

Farber and collaborators(1) therefore thought that an antagonist to folic acid if such a compound can be produced possibly might be able to inhibit the progression of the disease or even may check it. In collaboration with investigators in Lederle laboratories, they succeeded in producing a series of folic acid antagonists including aminopterin.

Experiment with aminopterin on animals demonstrated its inhibiting effects on mouse tumors and occasional cure of rat sarcoma(4,5,6). Hematologic lesions with changes in bone marrow and mucosa of the intestional tract such as are seen in severe folic acid deficiency were noted in mammals given the drug. Mice, rats, guinea pigs and dogs showed reduction of hematopoietic elements with destruction of bone marrow(7.8).

Mice with transplanted leukemia were treated with aminopterin

by Burchenal and co-workers(9). Survival times were prolonged although cures were not demonstrated.

Franklin and Franklin(10,11) found that a folic acid antagonist "X-methylpteroylglutamic acid," when fed to rats, mice, and chicks produced an acute deficiency syndrome which was reversed by increasing the dietary level of folic acid. 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.

Farber and his co-workers then began to use certain of these compounds in the treatment of acute leukemia(1,12,13). The first available compounds were pteroylaspartic acid (An-Fol-A) and methylpteric acid (Met-Fol-B), which they believed helped to prolong lives of a few children.

Beginning November 1947, 4-aminopteroylglutamic (Aminopterin) became available and the first impressive remissions in the course of acute leukemia were produced by the drug.

THEORY OF MODE OF ACTION OF FOLIC ACID ANTAGONISTS

Wooley(14) advanced a theory that previous experiments with anti-vitamin is valid for the folic acid antagonists, that is, the absolute amount administrated is of less significance than the ratio established between metabolite and anti-metabolite. Wooley has referred to this as the inhibition index. The antagonist

combines with the cellular enzyme protein so firmly that it cannot be displaced by folic acid, this leading to a deficiency.

Experimentally, folic acid antagonist has been found effective in significantly prolonging the survival time of mice with the Ak^4 strain of transplanted leukemia, although no direct cytocidal effect such as characterizes the use of nitrogen mustard, has been demonstrated(15,16). It has been shown that crude antagonist of folic acid caused a delay in appearance of immature cells in peripheral blood in normal mice and in Ak^4 leukemic mice it prevented any notable increase in either total white count or proportion of blast cells. In mice rendered folic acid deficient in this way the marrow is damaged and the erythroblast disappear (17,18,19). Using A-methopterin Burchenal(20) confirmed these findings and showed that in the usual therapeutic dosage it caused a slight leukopenia but no change in differential count in normal mice. In mice with Ak^4 strain of leukemia its use resulted in a prolongation of survival time, the leukocyte count remaining approximately normal levels, with reduction in numbers of abnormal cells and delay in the appearance of leukemic infiltration in the viscera and bone marrow.

In 1948, Sauberlich and Bauman(21) presented a paper on the relationship of folic acid and structurally similar antagonists. They described a factor necessary for growth of organism Leuconostoc citrovorum 8081, and Sauberlich(22) indicated a re-

lationship of this factor to folic acid.

Nichol and Welch(23) have demonstrated that in rat-liver slices the citrovorum factor is formed from folic acid in presence of certain reducing substance particularly ascorbic acid and that aminopterin both inhibits the substance particularly ascorbic ascid and that aminopterin both inhibits the conversion and competes with the products. These workers also found that, although folic acid would not prevent the lethal action of aminopterin on rats, the citrovorum factor completely counteracted the toxic effects of the antagonists.

Burchenal(20) have demonstrated that although the prolongation of the survival time of leukemic mice by the administration of A-methopterin can be partly experimentally prevented by simultaneous administration of folic acid, the effect of the A-methopterin is completely abolished by a small amount of the citrovorum factor. The citrovorum factor might therefore prove effective in countering the toxie effects on the leukemic cells.

Bethel(25) in studying the activity of aminopterin mentioned an interesting observation. The folic acid content of centrifuged leukocytes was examined. They were obtained from normal persons and from patients with chronic lymphatic leukemia, chronic myeloid leukemia, acute stem cell leukemia and acute myeloblastic leukemia; for each milliter centrifuged leukemic leukocytes the folic acid content was found to be respectively

40-180 microgram (ave. 80), 70-160(108), 75-220(146), 250-800(460). Furthermore, four cases of chronic leukemia there was a distinct fall in folic acid content of leukemic leukocytes in response to Xray treatment and this fall was simultaneous with reduction in the number of immature cells.

As yet it cannot be decided whether younger and more rapidly growing leukemic cells require larger amounts of folic acid than do the normal cells or whether the high folic acid content is due to defective utilization or some disturbance of folic acid metabolism. But it may be concluded from these observations that the folic acid content of leukocytes of peripheral blood is directly proportional to the degree of the immaturity of these cells.

Weber(27) thinks that aminopterin effect on leukemia is due to production of folic acid deficit, as perhaps the rapidly growing malignant cells are more sensitive to folic acid deficiency than are normal cells. Farber(1) and Dameshek(26) have advanced a similar theory.

This theory, however, does not appear quite convincing as Weber in contrast to Farber and Dameshek have not seen any aggravation after three to four weeks treatment with folic acid in these patients suffering from acute leukemia who had developed hematological and clinical remission following aminopterin treatment. Dameshek(26) claims tissure differs widely in their response with folic acid antagonists, and leukemic tissue may be

preferentially affected, therefore a "toxic reaction" may represent simply one or another aspect of therapeutic response on the cells in various parts of the body to folic acid antagonists.

PATTERN OF THERAPY

It is impossible at this time to present a pattern of therapy as definite that governing the treatment of diabetes or Addison's disease. Freedman(27) presented a paper giving the relative effective dosage. Aminopterin is given initially in dosage of .5 to 4 mgm. is given daily; A-methopterin 2 to 5 mgm.; amino-an-fol 25 to 75 mgm. daily with the dosage varying according to age and white blood cell count. Other authors gave somewhat the same dosage(13,28,29). For maintenance therapy aminopterin 0.25 to 1 mgm. is given daily, optimal maintenance doses of 0.5 mgm. aminopterin for adults and 0.25 mgm. daily for children(27). Farber(13) states that the effective dose when remission are obtained in children with acute leukemia lies between 3 and 5 mgm. a day for A-methopterin and between 25 to 50 mgm. a day for amino-an-fol. Because there is some differential in dose required to produce toxic reaction, as compared to effective dose it has been possible to shift from one drug to another when early signs of toxicity has become apparent(13,29).

Aminopterin may be given orally as well as by injection. Oral administration is as effective as parenteral therapy(13,26,

29,30,31). Smith(32), however, found that when the drug is given orally it is less consistent in its effect.

Weber(25) in giving maintenance therapy for acute leukemia, used an arbitrary schedule generally depending upon leukocyte count: count of over 50,000 per cmm. 1 mgm. of aminopterin; 2000 to 6000 per cmm. 0.5 mgm. of aminopterin and under 2000 per cmm. none.

The time period and dosage of the drug given before discontinuance varies each case(27,32). The chemical is injected or given orally until toxic reactions are evident or hematologic reaction occurs as evidenced chiefly by a drop in white blood count, following which the drug is discontinued(13,27,28,29,33).

Usually the drug is discontinued for five days to three weeks upon appearance of toxic reaction. After the reaction subsides or the white count has become stabilized at a lower level the drug is resumed in a maintenance dose. Maintenance therapy is continued except when a reaction takes place. If a relapse occurs the therapeutic pattern is repeated, increasing the dosage of the drug awaiting a reaction or response(27,28,33,34). For maintenance therapy certain group of workers gave the drug once daily(27,28); while other group of workers gave the drug two to three times a week(29,34).

Berman(35) found the total dosage to produce toxic effects varied from 30 to 105 mgm. (aminopterin). It was evident to him

that when small doses are used initially a larger cumulative dose can be tolerated before toxic symptoms appear.

Since an effective dose usually result in toxic reaction, it is possible that a therapeutic dose may require appearance of so-called toxic symptoms(26,27,34).

In general it may be stated that A-methopterin and amino-enfol are less toxic than aminopterin exactly the same toxic change may be produced when appropriate doses are employed(13).

Daily white counts, frequent platelet count, bleeding and clotting time and physical examination should be made when the drug is administrated(13,27,28,29,33). A patient with a leukocytosis of 70,000 to 100,000 cells per cm. may suddenly become leukopenia within a period of 24 to 48 hours(32,36).

Smith(32) thinks that bone marrow is most reliable mean of evaluating the drug therapy. This consideration is of especial importance because of the fact the peripheral white blood count in untreated leukemia of lymphoblastic is frequently normal or leukopenia through out the course of the disease. Furthermore the bone marrow may be excessively infiltrated with primitive cells which appear in such scant numbers in the peripheral blood as to be over look. Smith recommended that in addition to daily white blood count marrow aspiration should be made once a week.

Various type of supportive therapy has been attempted with no definite value in preventing or alleviating the reaction to the

drug. Most group of workers agreed that whole blood transfusion is effective in checking the hemorrhage, however only temporarily. Protamine sulfate, toluidine blue(25,30,32), rutin(33) failed to stop the bleeding. Penicillin and sulfa was found to be most effective in treating lesions of the oral cavity(25,29); other group of workers tried liver extract, folic acid or its derivatives with no satisfactory results(25,28,36,37). When the drug is withdrawn the toxic effect disappears.

RESPONSE OF THE LEUKEMIAS TO FOLIC ACID ANTAGONISTS

The clinical use of folic acid antagonist compounds has been extensively reported in human leukemia.

Price(38) treated eleven patients with aminopterin. Ten of these were children. He obtained complete remission in five patients who had acute leukemia. Two remissions lasted six weeks and three lasted less than one month.

Berman(35) treated nine patients with chronic leukemia by use of aminopterin. He found no subjective improvement in these patients. The use of the drug was limited by toxic reaction.

Kelich(40) reported a series of six patients who were treated with aminopterin, three were acute or subacute myelogenous leukemia; three early and two advance chronic myelogenous leukemia and one monocytic leukemia. There was no clinical improvement in any of these cases so treated.

Farber(1) reported results obtained by use of aminopterin in treatment of sixteen children with this disease. Ten of these showed clinical improvement and hematological improvement for a period of at least three monthes. In addition to its effect on the bone marrow, evidence of a beneficial effect on the leukemic deposit in the spleen and lymph nodes were found. Somewhat later Farber(13) reported over 50% of sixty cases showed significant effect directly attributed to the drug.

Jacobson(41) reported a series of four patients treated with aminopterin and six with A-methopterin. Beneficial clinical and hematological effects were obtained in one patient with each drug but toxic reaction were encountered in all patients receiving aminopterin. He felt that A-methopterin was less toxic than aminopterin.

Dameshek(26) reported on the results of treatment of acute and subacute leukemia; four children and thirty adult; eight died within five days after therapy started this left twenty-six cases of acute and subacute cases for evaluation of these nine had intermittent remission from two up to eight and half months. Best results were obtained in relatively subacute cases, fulminating cases were not effected. Of the subacute cases, the lymphoblastic cases respond the best, and none of the four monocytic type responded.

Wolman(42) in his paper on treatment of ten children with acute leukemia, with aminopterin over a period of two to six months;

seven remissions were reported.

Meyer(36) reported forty-three patients treated with folic acid antagonists. Of these, four patients showed improvement in hematological and clinical pictures. The remainder showed no changes or were adversely affected. Of the four patients who showed improvement, three were acute lymphoid type and one acute myeloid type. No beneficial results were noted in the adults. The cases with lymphoid leukemia responded more rapidly and precipitously with peripheral and bone marrow hypoplasia.

Wilson(37) in his survey of forty-eight human subject with acute leukemia treated with folic acid antagonist; there were nine of the twenty-five subject who responded to therapy who had initial thrombocytopenia. These were acute lymphatic leukemia in children ten years and under. Period of remission varied from 21 to 240 days.

Sacks(30) reported a series of fourteen patients with acute leukemia. Two cases had a complete remission. One of these was an adult patient with myeloid leukemia, the remission was 81 days. The other patient had a remission of 39 days. One monocytic fulminating case died in eight days after beginning of therapy.

Weber(25) treated 24 children, twenty out of the 24 had hematologic or symptomatic reversal of the leukemic picture. The drugs used in the treatment were A-methopterin and aminopterin.

Seaman(43) in his survey of sixteen patients of all type of tumors, approximately one-third of adults with acute and subacute

leukemia had remissions.

Hendricks(33) recently published a paper on the reults of treating ten patients. Six of these patients had acute lymphatic leukemia; two had remission, one three months; three had myeloid leukemia, one adult had a remission of three months; one adult had fulminating monocytic leukemia and died in eight days.

It will become evident on reviewing the cases reported that remissions are extremely variable.

The initial response was one of depression of bone marrow with reduction of all elements normal or abnormal. Very often aplasia develops after prolong treatment(25,28,33,40). The drug is withdrawn following the aplastic stage, the total leukocyte count rises gradually followed by a rise in reticulocyte and platelet count. This coinside with improvement of the patient(25,29,34,39). Weber(25) found a greater number of normal cells in peripheral blood was delayed, often not occuring until more than 75% of marrow cell were abnormal.

Clinical signs of remission are disappearance of generalized malaise, fever, weakness, pallor and hemorrhagic phenomena and repression of hepatosplenomegaly with the patient feeling and appearing markedly improved.

Hematologic indication of remission are development of normal white count, differential and platelet count; a marked reduction in blast cells in peripheral blood without transfusion. The

peripheral blood usually show changes within a few days after treatment is instituted. The white count often drops rapidly from high to low levels within two to three days(26,27,32,36). An initial low or normal count is no contraindication to therapy(27,33). Some particularly sensitive patients will show improvement in two to three days other longer(27,44). Price(39) found the effects to occur ten to twenty days after instituting therapy.

When the patient has toxic reaction with the drug he will feel worst and no apparent improvement or remission until the reaction subsides.

If the remission did not occur the patient usually felt somewhat improved but the leukemic signs became more prominent(44).

According to Farber(1) Diamond found spontaneous remission was considerable lower, 10% of leukemic children prior to institution of aminopterin therapy and in St. Louis hospital Cooke found spontaneous remission only in less than 1% of the cases. Jersild(29) found only 3% of sixty leukemic patient had spontaneous remission.

An outstanding response of the bone marrow was the production of megakaryocytes which were indistinguishable from these characterizing the erythropoiesis in Addisonian pernicious anemia in relapse(13,34,35,36,45).

TOXIC REACTION

Most group of workers stated that under this treatment stomatitis and gastrointestinal ulceration are frequent, often

accompanied by hemorrhage and fever(28,29,36,37,43). Mills(34) found such in more than one-half of twenty-one cases treated. It may be claimed that the gastrointestinal hemorrhage constitute part of the leukemic picture, but the nature and extent usually exceed the finding in untreated cases of leukemia(29).

Diarrhea is not rare but usually disappears rapidly when treatment is discontinued(27,35,39).

Instances of alopecia have been reported(27,29,30,34,35,36). Regrowth of hair occurs even with continuation of therapy(29).

Many workers found inhibition of marrow with reduction in both normal and abnormal marrow element(25,28,33,40). Meyer(36) and Mills(34) found the hypoplasia of bone marrow most serious toxic reaction.

After taking the drug for several months, generalized brownish pigmentation of skin may appear which persist even though the drug is discontinued(27). Weisman(46) claimed the hyperpigmentation is due to a process of melanogensis within the epidermus.

A hemorrhagic rash(27,33), an apparent aggrevation of bleeding tendency often occurs(29,36,38,47).

The toxic reaction usually appeared between five day to three weeks after initiation of therapy. The first symptoms usually was stomatitis, then gastrointestinal disturbance with diarrhea and rectal hemorrage. These symptoms progress on continue therapy. The stomatitis will lead to ulceration of buccal mucosa, if

therapy is continued(27,35,39). Meyer(36) states that in a few patients with buccal mucosal lesions appearing early in course of therapy and of mild character, the drug was continued and no further progression was noted of these lesions.

The "toxic reaction" disappears when the drug is removed.

CAUSE OF HEMORRHAGE

In and attempt to determine the cause for bleeding, Weber(25) noticed that the bleeding was associated with a thrombocytopenia and did not occur unless thrombocytopenia was present. The use of protamine sulphate or toluidine blue failed to influence the bleeding and was considered to be evidence that hyperheparinemia did not contribute to the hemorrhagic tendency. Sacks(30) found that the prothrombin level remained normal until the terminal phases. It was difficult to determine whether the thrombocytopenia was the result of the leukemic involvement of the bone marrow or result of platelet production by the antagonist.

In contrast to Weber, Allen and Jacobson(48) showed that in many children with acute leukemia the level of heparin-like substance in blood is definitely higher than normal. While bleeding occurs usually when the level of blood platelets is low; thrombocytopenia may be present without evidence of bleeding for many months and occur more readily when marrow is depressed.

Cereveld(47) demonstrated that after administration of aminopterin

there is a decrease of plasma Ac-globulin which is the cause for excessive hemorrhage in patients treated with folic acid antagonists.

CRITERION FOR REMISSION

There has been no definite standard for determining remissions of leukemia. Various workers have different views concerning the criterion for remission. We will therefore present the views of the different groups of workers.

Freedman(27) felt that continuous improvement should occur for at least two months before it is considered a definite remission. He also reported that the rise of platelet count to normal when it is initially low is one of the best signs of remission, and they are usually the last elements in the blood to respond.

Mills(34) definition for a remission is given as one to three months of clinical hematological improvement.

Dameshek(26) stated that a definite increase on blood platelet must be considered as part of criteria in determining whether or not a remission has occurred.

Rhoades(49) and Smith(32) suggested that the term remission properly should be reserved for essentially complete restoration of normal hematologic function and health in all other respect. Strict application of the term hematologic remission therefore implies a restoration from an abnormal to normal bone marrow pattern

and peripheral blood smears in which "blast" cells appear in appreciable numbers cannot be regarded as indicative of remission. Short of these hematologic goal "improvement".

MECHANISM OF RESISTANCE

There is a general agreement that the remission induced in patients with leukemia by folic acid antagonists are only temporary and that the disease eventually become resistant to this form of therapy.

Burchenal(50) demonstrated an analogous situation in mouse leukemia, although survival time of the treated mice may be more than doubled, all eventually die of the disease despite continuous therapy. It has been possible by methods somewhat similar to those used in producing drug fast strain of bacteria, to develop a subline of leukemia completely resistance to therapy with folic acid antagonist. This was accomplised by several serial passages of the leukemia through treated mice. In this subline no significant increase in survival time could be produced by therapy. This characteristic resistance has remained fixed despite ten passages through untreated animals.

In conclusion, Burchenal gave three theortical explanations. They are as follows: The ability of resistant leukemic cells to synthesize its own pteroylglutamic acid; to deaminate the antimetabolite thus producing folic acid; an increased ability of host organism to detoxify the compound.

A REVIEW OF THE CASES OF LEUKEMIA TREATED WITH FOLIC ACID ANTAGONIST AT UNIVERSITY OF NEBRASKA AND CHILDREN'S HOSPITAL

Case I.

Patient W.B. white female, age 6 months

Admitted 5/29/50

Chief complaint: Abdominal swelling, two months duration.

Physical examination: The patient was well developed, well nourished baby in no apparent distress. There were some small nodes in the right suboccipital area. The abdomen was markedly distended with marked venous congestion around the umbilicus. The liver was palpable below the iliac crest. The spleen was down 4 to 5 cm.

Lab. examination: On 5/29/50, the wbc. 72,000, staff 2%, young 3%, lymphocytes 66%, monocytes 2%, immature lymphocytes 1%, and broken cells 25%, platelet count 134,000. The child seemed to develop some dyspnea and was given some radiation which brought the white blood count down to 24,500. On 6/7/50, the child received 40cc. of blood and again on 6/8/50. The temperature was very irratic throughout the hospital cours and varied from normal up to 103.0 practically every day. On 6/15/50, the child was started on aminopterin 0.5 mgm. daily. On 6/19/50 the wbc. dropped rapidly to 5,000 from 111,000 on 6/16/50. The drug was discontinued the next day, 6/20/50. The count dropped to 2,500 the following day and continued to run approximately 2,500 thereafter.

The child was given several more transfusions and excessive bleeding was noted from the mouth, nose and any wound. Bone marrow was compatible with subacute leukemia. Bleeding tendency increased daily, the platelet decreased to 72,000. Bleeding from nose, mouth continued and the child died chiefly from exsanguination 6/27/50.

Case II.

Patient S.E. white female, age 8

Admitted 4/7/50

Chief complaint: Swelling at the angle of the jaw since 3/28/50 and gradually enlarged. The patient was pale, lost appetite, sore throat and temperature 102.0.

Physical examination: The patient appeared pale, acutely ill, throat red including tonsils and tongue. There was lymphadenapathy bilatel, anterior cervical chain of neck. The spleen was palpated 3 cm. below the left costal margin. The liver was palpated just below the right costal margin. There was moderate tendor adenopathy in each axilla and in the inguinal regions. Epitrochlear nodes were palpable.

Clinical course: The bone marrow was diagnostic of subacute lymphatic leukemia and the patient was started on aminopterin 4/11/50. She was given 1 mgm. for 7 successive days. On 4/24/50, she was given 1 ampule vitamin B12 and on 5/2/50, she was given aminopterin again, 1 mgm. daily until 5/8/50 when it was changed to 1 mgm. every other day. This was continued until dismissal, 6/3/50.

She was also given 2 more ampule of B12. On admission, her temperature was 102.4 rectally and she continued to spike a similar temperature almost every day until dismissal with occasional episodes of 3 or 4 days when she would be afebrile towards the end of her hospital course. Her adenopathy gradually decreased. The spleen was still palpable though somewhat smaller, on dismissal. The toxic reaction were sore tongue, anorexia. Macrocytosis was also noted. On dismissal, the patient was put on maintenance therapy 1 mgm. aminopterin daily, and followed in outpatient clinic.

Lab examination: Hemoglobin on admission was 9.0 grams rbc. 2.78 million. There were 4,100 leukocytes with 5% segs., 10% staff, 80% lymphocytes, 3% monocytes and 2 irritation lymphocytes. There were approximately 3 nucleated red blood cells per 100 white blood cells. Successive count showed a gradual decrease in red and white cells to a low on 4/25/50 of 5.6 grams of hemoglobin, 1.84 million red cells, 1,500 lymphocytes with 4% segs., 5% staff, 89% lymphocytes, 1% monocytes and 2 irrigation lymphocytes. This was treated with blood and vitamin B12 with a favorable response. The leukocyte distribution gradually changed until on 5/2/50, she showed 9.0 grams of hemoglobin with 3.22 million red blood cells, 4,100 leukocytes, with distribution of 25% segs., 3% staff, 69% lymphocytes, and 3 monocytes. Platelet count on 4/10/50 was 115,000 with reticulocyte count of .3%. This was frequently repeated and on 4/28/50, the platelet count was 71,000 and the

reticulocyte was 4.2%. On 6/2/50, the platelet count was 120,000 and the reticulocyte count 1.6%, there was no convincing abnormalities seen in the long bones by Xray. The mandible and adjacent bones showed no evidences of leukemic involvement.

The sternal bone marrow was compatible with that of subacute lymphatic leukemia.

The patient admitted again on 8/11/50 with a relapse. This time she was treated with cortisone and had two subsequent remission on cortisome.

The patient expired 2/9/51.

Case III,

Patient L.L. male, age 10

Duration of disease 3 months

Clinical diagnosis: Acute granulocytic leukemia.

Laboratory examination: Peripheral blood smear 37,000 wbc., 22% segs., 11% staff, 1% myelocytes, 50% blasts, 15% lymphocyte, 1% monocytes, 1.8 million rbc., 6.1 grams of hemoglobin, platelet count 16,000. Bone marrow examination revealed dimination of the megakarocytes, depression of erthropoiesis and marked hyperplasia of granulopoiesis with increased blasts and maturation arrest at the metamyelocyte level.

Aminopterin was the drug used, 0.5 mgm. every day. Duration of therapy 9/7/50 to 9/18/50, total dose 6 mgm.

Clinical Course: Toxic reaction consisted of anorexia and late

vomiting. Supportive therapy consisted of whole blood during aminopterin therapy. No definite alteration of the course of the disease was noted. The patient died on 9/22/50 from bleeding with 5,000 to 15,000 platelet count throughout his illness. Follow up marrow should slight reduction in cellularity and total wbc. fell from peak of 70,000 to 44,000 prior to death. Post mortem revealed acute leukemia with chloromatous infiltration of ribs and calvarium.

Case IV.

Patient P.C. male, age 10

Duration of disease 11 months

Clinical diagnosis: Acute lymphatic leukemia.

Lab. examination: Peripheral blood smear, 2/5/51, hemoglobin 8 grams, 2.8 million rbc., 7,100 wbc., 3% segs., 5% bands, 1% metamyelocytes, 1% eosinophiles, 27% prolymphocytes, 63% lymphocytes. The platelets were markedly diminished. Bone marrow examination 2/7/51 showed that the marrow was nearly completely replaced by lymphocytes, prolymphocytes, and lymphoblasts, the latter predominate. Xray, August 1951, demonstrated leukemic infiltration in the long bones of lower extremities.

Cortisone 100 mgm. was given daily from 7/15/51 to 8/1/51 then 2 weeks on tapering doses.

Aminopterin and A-methopterin were the drugs used. Total dose aminopterin, 51 mgm.; A-methopterin, 35 mgm.; duration of therapy 2/51 to 11/51.

Clinical course: Toxic reaction consisted of slightly sore tongue, occasional anorexia and diarrhea; macrocytosis was noted. Supportive therapy consisted of whole blood and antibiotics. The patient course seemed altered as evidenced by the absence of petechial hemorrhage and the presence of thrombocytes. He had no platelets and had petechial hemorrhage at first visit in February. This cleared up and did not reoccur until late in August. Improvement occurred with cortisone at this time. In late October gross hemorrhaging occurred and he was treated with aminopterin and antibiotic, and no blood. Again the bleeding stopped. However, the patient developed a fulminating pneumonia and died 11/13/51. No post mortem was obtained.

SUMMARY

Clinical trial with folic acid antagonists followed soon after the discovery that folic acid deficient state produced changes in tumor growth in animals and the acceleration of the leukemic process by folic and related compounds. Beginning November 1947 the first impressive remissions in the course of acute leukemia were produced by the drug.

The theory of mode of action of folic acid antagonist has not been definitely established, however, the following theories have been advanced: "Competitive metabolic inhibition" somewhat like that of the theory governing the action of sulfa drugs on bacteria; Leukemic cells are more sensitive to folic acid deficit; Tissue differs widely in response to folic antagonist and leukemic tissue may be preferentially affected.

The pattern of therapy, though somewhat variable, generally consist of bone marrow aspiration before therapy is began; daily white and differential count; red blood cell and platelet count, and hemoglobin during the administration of the drug. The drug most commonly used is aminopterin. The dose varies from 0.25 mgm. to 1 mgm. daily depending on age and weight. Children are generally given 0.5 mgm. daily. The drug is given orally or intramuscularly. The drug is discontimued on first sign of toxic reaction since the effect of the drug is cumulative or when there is a precipitous drop in white blood cell count which can occur within 24 to 48 hours.

When the blood count is stablized at a low level 6,000 to 30,000 the patient is put on maintenance therapy. Bone marrow aspiration is made when there is a change in peripheral blood picture or once a week when on maintenance therapy is recommended by some group of workers. On maintenance therapy, children are given 0.25 mgm., adult. 0.50.mgm.

The toxic effect of the drug is the most serious drawback for its use. Increase tendency to hemorrhage is the most common toxic effect. Stomatitis frequently appears first, then gastrointestinal symptoms accompanied by hemorrhage. Diarrhea, alopecia also has been reported. On prolong therapy irreversible aplasia of bone marrow may occur.

The response of the leukemia to the drug is variable and each case responds differently. The drug is most effective in subacute lymphatic leukemia, followed by acute lymphatic leukemia. It is the least effective in the monocytic leukemia. Chronic leukemia responds occasionally, however, the response could be due to the natural tendency for an occasional remission to occur. Natural remission as reported by different group of workers varied from 3% to 10%. Since the use of folic acid antagonist, remissions averages about 30%. On relapse, the leukemic cells become more resistant and eventually the leukemic process takes over and the patient dies.

Criterion for remission varies among workers, however, most workers agree that the patient should subjectively feel well and

have a normal hematological picture.

Burchenal presented a paper giving several possible theories for mechanism of resistance. These are as follows: The ability of resistant leukemic cells to synthesize its own folic acid: To deaminate the anti-metabolite thus producing folic acid; An increase ability of host organism to detoxify the compound.

CONCLUSIONS

It is obvious that no two children with acute leukemia present strictly a comparable problem. Less than 10% have spontaneous remission and these are of variable lenghth averaging about 10 weeks. Infiltration in the leukemic process is generalized but there are great variations in the degree and site of involvement. In one, a large subdural accumulation of tumor may alter intracranial pressure to an important degree; in another the leukemic infiltration in the heart may be responsible for unexpected death. Other variables are the replacement of bone marrow by leukemic cells. It should not be surprising, therefore if one research group report five consecutive remissions, or that another group observes a fatal outcome within two weeks after onset of therapy in ten consecutive patients before one remission is observed. Some of the workers have been given inadequate dosage of the drug. Few of the workers have used crude folic acid antagonist. It is possible that certain cases were not observed as minutely as seem necessary.

The criterion for a remission is different from one group of workers to another.

The duration of remission is extremely varible although maintenance therapy is given, a relapse usually occurs which might not respond to increase dose.

The most striking finding in the study were the unpredictability

of the action of the drug. Both beneficial and toxic effect could not be controlled nor could these effects be related to dosage of the drug alone or to its administration simultaneously with liver extract, folic acid or other supportive measures.

The use of folic acid antagonist has appreciable altered the course of leukemia in children. It has prolonged the life of many patients, affording them additional months of confortable and frequently normal life. The ultimate outcome has not been influenced.

All patients who died after treatment over a long period, an autopsy have scant, if any evidences of leukemia suggesting aplastic anemia rather than leukemia.

Any evaluation of treatment of patients with incurable cancer must rest upon a solid foundation of knowledge concerning the life history and biologic behavior of tumors. Acute leukemia which run an inveriably fatal course varying from a few weeks unually to six months after onset of symptons lends itself readily to comparative studies. Rarely the course may last a long as twelve months and isolated instances of longer survivals have been observed. The end point of time itself, therefore, should serve as a reliable criterion of value of any form of therapy.

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