THE TREATMENT OF LYMPHOBLASTIC LEUKEMIA WITH CRUDE MYELOKENTIC ACID

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Evidence has been presented previously that myelokentic acid and lymphokentic acid are present in varying amounts in the urine of patients with acute and chronic leukemias, Hodgkin's disease, and lymphosarcoma. We reported in 1940 that partial remissions occurred in 2 patients with lymphoblastic leukemia during periods in which they were receiving injections of extracts of the urine from patients with chronic myeloid leukemia. At that time it was postulated that patients with lymphoblastic leukemia lacked the stimulus for myeloid proliferation. Later evidence was given that substantiates the hypothesis of a balance between myeloid and lymphoid cell production.

The present paper reports 12 cases of lymphoblastic leukemia. To 8 of them we have given extracts of urine or feces from patients with chronic myeloid leukemia. The other 4 cases are reported as controls. Necropsies were performed on 5 of the 8 treated cases and on all 4 untreated cases. A comparison is drawn between the clinical course and pathologic morphology of treated and untreated cases.

No patients were especially selected either for treatment or for use as controls. All were relatively young individuals, the oldest being 30 years of age in the untreated group. The treated group ranged from 21/2 years of age to 15 years of age.

All patients, treated or controls, were given blood transfusions when necessary. Bone marrow aspirations were done in all instances in order to ascertain the extent of the disease. In some of the treated cases bone marrow aspirations were repeated when partial remission occurred. Four of the patients were treated with either sulfadiazine or penicillin when infection occurred.

The crude myelokentic acid that was used was extracted either from urine or feces of patients with chronic myeloid leukemia. The extracts were made by methods we have described. Chloroform extract of hydrolyzed urine was used in the treatment of 5 cases. Chloroform extract of feces was given to 1 patient, and to 2 patients the hydrolyzed eluate of kaolin adsorbate of urine was given. When the latter was used the dose was increased ten to fifteen fold because of the difference in potency of the material as determined by assay on guinea pigs.

CASE REPORTS

Case 1. J. H., a 5 year old white girl, had whooping cough in November 1938 and shortly afterwards it was noticed that she was pale. From January 1939 to October 1939 she received four blood transfusions. She entered the Jefferson Hospital in October 1939 because of a persistently low leukocyte count. A sternal marrow aspiration and a biopsy revealed marrow made up largely of lymphoblasts. She was given several transfusions, liver extract, and vitamins. The leukocyte count varied from 850 to 4,500. The spleen and liver were both palpable at all times and there was some enlargement of all peripheral lymph nodes. Because it was thought that she might have splenic neutropenia, a splenectomy was done 12-4-39. The spleen weighed 130 grams and two accessory spleens were found and removed. The splenic pulp consisted largely of lymphoblasts.

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During the four weeks following splenectomy a mild remission occurred, and normal blood cell elements appeared in the peripheral blood. A bone marrow aspiration three weeks after splenectomy revealed nearly normal hematopoiesis. On 1-11-40 relapse was evident. At this time the leukocyte count had dropped from 7,000 to 1,000 and lymphoblasts were occasionally found in the peripheral blood. On January 13 she was given the first dose of crude myelokentric acid. This was the chloroform extract of hydrolyzed urine, and it was given in alkaline water at pH 7.5 in doses of 1 or 3 cc. every other day; each cc. represented 160 cc. of urine. With each injection of myelokentric acid 1 to 3 units of liver extract were given. At the end of two weeks the leukocyte count was being maintained at or above 4,500 per cu. mm., with 30 per cent polymorphonuclear neutrophiles. At this time she was given no extract for seven days and the leukocyte count fell to 2,000 per cu. mm. Treatment with the extract was resumed in doses five days apart till 1-15-40, when daily doses of 1 to 1½ cc. were given for the following four weeks. Throughout this time she appeared to be well into remission. The bone marrow had again approached normal in cellular elements and the leukocyte count and erythrocyte count were well maintained. On 3-11-40 active material was stopped and the inactive neutral fraction of urine extract was given instead. Injections of this were given in oil and she received an amount equal to 500 or 750 cc. of urine daily for six weeks. By the end of the fifth week of this treatment lymphoblasts again appeared in the blood stream, lymphocytes increased in percentage, and the polymorphonuclear neutrophiles decreased. On 4-25-40 active material was again started and was continued for four weeks, but during this period she continued to go deeper into relapse. The leukocyte count remained high, 10,000 per cu. mm., and 40 per cent of the cells were lymphoblasts. The last sixteen days of her life she was again given the inactive neutral fraction of urine extract. The leukocyte count reached 60,000 but dropped to 1,200 the day before she died. Death occurred 6-9-40 and a necropsy was performed.

Case 2. S. G., a 15 year old white boy, entered Jefferson Hospital 1-15-40 because of pallor and pains in his legs and back. He had become ill early in November 1939. In December of that year he was admitted to a hospital where anemia was found and one transfusion was given. On entry to Jefferson Hospital the liver and spleen and all peripheral lymph nodes were moderately enlarged. The leukocyte count was 12,000 per cu. mm., 80 per cent of which were lymphoblasts. The erythrocyte count was 1,200,000 and hemoglobin 28 per cent. A bone marrow aspiration revealed a very cellular marrow made up almost entirely of lymphoblasts (fig. 1). The spleen, liver, and thoracic lymph nodes were enlarged clinically and were determined to be so by roentgenogram. On 1-19-40 an initial dose of crude myelokentric acid was given and this was followed by daily doses of 2 cc. (1 cc. equaling 400 cc. of urine). It was administered in alkaline water solution at a pH of 7.5. This was continued, with but few exceptions, daily until 3-8-40. One to 3 units of liver extract were given with nearly every injection of the urinary extract. During the first four weeks of this period he had many furuncles and abscesses on his arms and legs and his temperature varied from 100° to 104° F. Blood transfusions were given when necessary. In the first three weeks of this period three blood cultures were reported to show no growth in forty-eight hours, and agglutination tests for typhoid organisms were negative.

The leukocyte count fell from 12,000 to 300 during the first four weeks of treatment and the lymphoblasts decreased in percentages as well as in number, while mature lymphocytes appeared in the low counts. After the marked leukopenia of 300 was reached, the leukocyte count slowly began to rise and as it rose normal lymphocytes of both the myeloid and the lymphoid series made up the blood picture. On 3-8-40 the leukocyte count was 3,400 and the differential count was 36 per cent neutrophiles, 35 per cent metamyelocytes, 27 per cent normal lymphocytes, and 2 per cent monocytes. A blood culture taken on 2-29-40 was reported 3-4-40 as positive for paratyphoid B. Because of this and because it was felt that if he had true leukemia relapse would recur, treatment with myelokentric acid was discontinued. Blood transfusions were not necessary for a period of two months. The spleen and liver had reduced in size clinically as well as radiographically. Furuncles and abscesses were almost entirely healed and he was up and about the ward. A bone marrow aspiration 3-28-40 revealed partial regeneration of the myeloid elements (fig. 2). He remained in good condition, but on 4-1-40, 4 per cent lymphoblasts were found in his peripheral blood. On this date an injection of inactive neutral fraction of urine extract was given and similar injections were given daily for three and one-half weeks. This material was given in 1½ cc. alkaline water emulsion. (One cc. was equal to 1,000 cc. urine.) During this injection period his relapse increased. There was an increased size of lymph nodes and spleen, and a shift to 50 per cent lymphoblasts in a
Leukocyte count of 8,000 on 4-27-40. He again had fever, and blood transfusions were again necessary because of the recurrence of anemia. Injections of crude active myelokentric acid were again started on 4-24-40. These were continued daily for four weeks and a second remission began. There was again a marked drop in the leukocyte count to 1,100 cells and diminution in the percentage and number of lym-
Case 2. E. S., a 9 year old white boy, entered the Jefferson Hospital 8-28-40 because of a "lump" on the side of his neck. This had been present for one month. He had lost 3 pounds in weight and had a low grade fever for two weeks. All peripheral lymph nodes, the liver, and spleen were enlarged. The leucocyte count was 11,000, differential count was 6 per cent polymorphonuclear neutrophiles, 13 per cent lymphocytes, 7 per cent metamyelocytes, 74 per cent lymphoblasts. The erythrocyte count was 3,400,000, hemoglobin 61 per cent, and the platelets were not reduced. A sternal marrow aspiration revealed a very hyperplastic marrow with 90 per cent lymphoid cells, and of these 60 per cent were lymphoblasts. The leucocyte count on 9-3-40 was 23,000 with the same differential count and on this day an initial dose of 1 cc. of crude myelokentric acid was given to him by intramuscular injection. One cc. of this material was equal to 500 cc. of urine. This was the chloroform extract of hydrolyzed urine and it was made up in alkaline water solution at a pH of 7.5. This amount was given daily for eleven days. At this time the dose was increased so that 1 cc. of extract was equal to 750 cc. of urine. Two cc. were given daily until 10-20-40, when a further increase in the dose was made so that he received 3 to 3½ cc., each cc. of which was equal to 1,000 cc. of urine. This latter dose was continued until 11-12-40 and after this date the extract was made up into capsules. These were given orally, fifteen each day, and this dose was equal to 2,800 cc. of urine. This was continued until 1-5-41.

On 9-13-40 the leucocyte count had risen to 44,000 but the percentage of lymphoblasts was reduced to 52. Slowly the leucocyte count fell and on 10-7-40 it was 9,000. The lymphoblasts had decreased to 24 per cent. At this time there was little decrease in the size of the lymph nodes, spleen, or liver, and clinically, improvement was slight. He was discharged from the hospital on 9-30-40 but injections were continued while he was at home. He was readmitted to the hospital 11-1-40 and was given three blood transfusions. On 11-16-40 the lowest leucocyte count was reached; it was 4,500. The differential count at this time was, polymorphonuclear neutrophiles 6 per cent, lymphocytes 55 per cent, metamyelocytes 13 per cent, myelocytes 4 per cent, lymphoblasts 21 per cent. He was discharged from the hospital again on 11-26-40 and was cared for at home. In January, when treatment with the extract was discontinued, the leucocyte count was 17,000, erythrocyte count was 2,500,000, and the hemoglobin was 49 per cent. The differential count was polymorphonuclear neutrophiles 5 per cent, eosinophiles 1 per cent, lymphocytes 49 per cent, metamyelocytes 8 per cent, lymphoblasts 37 per cent. No further therapy was given, including transfusions, but he was observed until death on 3-10-41. Permission for a necropsy was not obtained.

Case 3. R. W., a 2½ year old white girl, entered Jefferson Hospital 6-8-42. She had been ill for two weeks during which time her mother had noticed pallor, black and blue spots on her skin, and a loss of appetite. The spleen was enlarged 3 centimeters below the costal margin, the liver was slightly enlarged, and there was generalized lymphadenopathy. On 6-10-42 the erythrocyte count was 3,300,000, hemoglobin 50 per cent, the leucocyte count was 75,000, and the differential count was polymorphonuclear neutrophiles 1 per cent, lymphocytes 53 per cent, monocytes 5 per cent, lymphoblasts 40 per cent. With the exception of one period, i.e., from August 6 to August 21, this child was given various extracts and fractions of extracts of feces from patients with chronic myeloid leukemia. She was given ½ cc. to 1 cc. injection daily, usually in oil of which the fecal equivalent was about 75 to 100 grams. During the period of August 6 to August 21 she was given ½ cc. to 1 cc. of urinary extract daily, 1 cc. equaling 1,000 cc. of urine. The fecal extracts were made up every two weeks; their potency was not known. The marrow from a bone marrow aspiration prior to treatment consisted almost entirely of lymphoblasts. The first twelve days that she was in the hospital the leucocyte count fell to 1,800 and the lymphoblasts completely disappeared from the blood stream. A second bone marrow aspiration at this time revealed an increase in myeloid elements in the marrow. The platelets increased in the blood stream from 56,000 at entry to 146,000 on 6-13-42.
The lymph nodes, spleen, and liver reduced in size and she was clinically improved. On 6-17-42 her peripheral blood showed 30 per cent myeloid white cells, 68 per cent lymphocytes, and 2 per cent monocytes and no lymphoblasts. On July 6, however, her leukocyte count had increased to 40,000 with 16 per cent polymorphonuclear neutrophiles, 81 per cent lymphocytes and 3 per cent lymphoblasts. Through July and into August her leukocyte count varied from 12,000 to 71,000 with large numbers of lymphocytes and only a few lymphoblasts. During the period in which she received urinary extract the leukocyte count remained high. The week after this was discontinued, however, and fecal extract was again used the leukocyte count decreased to 800 cells with 92 per cent lymphocytes. The leukocyte count then rose to 4,300, and on 9-16-42 the reticulocyte count was 6.5 per cent and the platelet count was 100,000. At this time there were 49 per cent polymorphonuclear neutrophiles in the peripheral blood.

She again relapsed completely and the leukocyte count rose to 156,000 but contained only a small number of lymphoblasts—1 per cent. The lymph nodes and spleen remained reduced in size throughout the entire course of her illness after treatment was started. She died 10-10-42. The leukocyte count the day of death was 500. At this time she had a papular eruption over her entire body which might have been due to septicemia, but no blood culture was taken. A necropsy was performed.

Case 5. L. R., a 23 year old white girl, entered the hospital 7-12-44. She had lost 2 to 3 pounds in weight, was pale, and had had anorexia for six weeks before coming to Jefferson Hospital. She had been in another hospital the two weeks before entry at Jefferson and had received two blood transfusions. The spleen and all peripheral lymph nodes were moderately enlarged and the leukocyte count was 15,000, of which 59 per cent were lymphocytes, 40 per cent were lymphoblasts, and 1 per cent were polymorphonuclear neutrophiles. The erythrocyte count was 1,600,000, hemoglobin 48 per cent, and the platelet count was 12,000. A bone marrow aspiration revealed marrow made up almost entirely of lymphoblasts. For eleven days she was given 10 cc. or 100 units daily of adrenal cortical extract. This was done in order that we might have a period of control before the urinary extracts were administered. Throughout this period there was no improvement clinically nor was there a change in her blood cell elements. The period between 7-15-44 and 8-22-44, or for twenty-four days, she received 3/4 cc. to 1 cc. of urinary extract daily (1 cc. of which was equal to 4,000 cc. of urine). This material was the chloroform extract of the hydrolyzed alcoholic eluate from kaolin adsorbate of urine. The larger dose was used because this was not as potent as the chloroform extracts of hydrolyzed urine. Because of a lack of urine from August 12 to 28 she received the extract from only 2,500 cc. of urine daily, but after that the dose was again increased to 6,000 or even 12,000 cc. daily. On 7-24-44 the leukocyte count was 14,000 with 87 per cent of the cells lymphoblasts, after which it gradually fell so that on August 5 it was 3,300 and the lymphoblasts were only 14 per cent. On August 17 the leukocyte count was 5,000; the differential count was 9 per cent polymorphonuclear neutrophiles, 1 per cent eosinophiles, 1 per cent myelocytes, 88 per cent lymphocytes, and 0 lymphoblasts. Throughout this period her erythrocyte count was maintained at or above 3,000,000 without transfusions of blood. However, she gradually slipped into relapse again and on September 4 had 78 per cent lymphoblasts in a leukocyte count of 60,000. On September 17, and 18, and 20 she was given a total of 300 r of x-ray over neck, thymus, and spleen with the hope that this plus the urinary extracts would control the leukemic process. The leukocyte count then fell to, and remained under, 1,000 from September 25 to October 1, the day of her death. A middle ear infection was controlled during her hospitalization by penicillin.

In the last week of her illness she developed an abscess of her right buttock and penicillin was given to control this. She died 10-2-44 and a necropsy was performed.

Case 6. D. H., a 4 year old white boy, had been ill for five months when he entered Jefferson Hospital 9-28-45. He tired easily and had had anorexia throughout this time. He was irritable, pale, and had evidently lost a little weight. The axillary, cervical, and inguinal lymph nodes were enlarged. The abdomen was protuberant because of enlargement of the spleen and liver. The erythrocyte count was 810,000 and the leukocyte count was 9,500. The platelet count was 30,000, and the differential count revealed 41 per cent lymphocytes and 49 per cent lymphoblasts. He was given a blood transfusion and injections of urinary extract were begun. This extract was the hydrolyzed eluate from kaolin adsorbate urine. The first twenty-five days he received material daily from the same lot of extract. Each injection was equal to from 5,000 cc. to 20,000 cc. of urine. From September 26 to October 17 he received four blood transfusions. The
leukocyte count slowly decreased until on October 13 it had reached 1,500. Lymphoblasts at this time were only 12 per cent of the total count. The lymph nodes and spleen became smaller and he began to have a better appetite. On October 12 he had a sore throat, for which penicillin was given. After his throat became well the leukocyte count gradually increased to between 3,000 and 5,000 but the lymphoblasts remained low in number. The platelet count increased to 54,000 and the erythrocyte count was maintained at 3,000,000 without a blood transfusion for five weeks.

He was given injections of the same type of extract from a different lot beginning 10-17-45, but he received only an amount equal to 1,500 cc. of urine daily. This was continued for sixteen days and was then doubled in amount for six days, but on 11-15-45 chloroform extract similar to that given to cases 1, 2, and 3 was administered in doses of 1 cc. daily (each cc. was equal to 1,000 cc. of urine). This was continued until seven days before his death. During the last three weeks of his life he was obviously in relapse, with a leukocyte count as high as 35,000 cells, of which 81 per cent were lymphoblasts. The leukocyte count, however, fell during the last week of his life and was 1,700 the day of his death. He had developed an abscess of the left buttck which was incised and following this he bled from the wound and from the nose and throat. Staphylococcus aureus was cultured from the abscess. Death occurred on 12-2-45 and a necropsy was performed.

Case 7. A. B., an 11 year old white boy, entered Jefferson Hospital 12-14-45. He had been ill for one year. His illness started with joint pains and fever. In March 1945 a diagnosis of leukemia was made because of a leukocyte count of 20,000 which contained large numbers of lymphocytes and lymphoblasts. At that time his erythrocyte and platelet counts were low. Throughout the year he had received at least one transfusion of blood a week. The leukocyte count at one time was nearly 100,000. He had several attacks of middle ear infection and many attacks of joint pains simulating acute rheumatic fever. He had lost a great deal of weight and weighed only 40 pounds when admitted to the hospital. On 12-14-45 the leukocyte count was 55,000, and the erythrocyte count was 1,800,000, with hemoglobin of 35 per cent and the platelet count was 10,000. The differential count was polymorphonuclear neutrophiles 1 per cent, myelocytes 1 per cent, small lymphocytes 6 per cent and lymphoblasts 91 per cent. A bone marrow aspiration had been done elsewhere and the marrow was made up largely of lymphoblasts although it was not very cellular. He was treated with chloroform extract of urine (1 cc. of which equaled 1,200 cc. of urine) administered by intramuscular injection in doses of 1 cc. daily for nineteen consecutive days. The last two days of his life this was not given. Along with this he received 3 units of liver extract daily and a total of five transfusions of blood. He had a middle ear infection which yielded to treatment with penicillin. The leukocyte count decreased to 1,600 the day of death but the percentage of lymphoblasts remained at about 90. Six days before death he passed bloody urine and from then on he bled from the urinary tract, from the nose, and from the bowel. He died 1-7-46 and a necropsy was performed.

Case 8. R. H., a 14 year old white boy, entered Jefferson Hospital 5-2-46. For four months he had complained of easy fatigue and a loss of weight. For about four years he had been using lacquer and quick-drying airplane glue in building model airplanes. These probably contained benzol. In December 1945 he had had a severe "cold" and since that time had had weakness, joint pains, nosebleeds, and anorexia. At another hospital during a six week period he received twelve blood transfusions. At that time a bone marrow aspiration had shown a marrow that was very cellular and contained large numbers of lymphoblasts.

On entry to Jefferson Hospital examination disclosed the spleen and liver to be palpable at the rib margins, and there was generalized slight lymphadenopathy and pallor. The erythrocyte count was 2,600,000, hemoglobin 59 per cent, and the leukocyte count was 6,300, and the platelet count was 10,000. The differential count was polymorphonuclear neutrophiles 10 per cent, lymphocytes 55 per cent, lymphoblasts 35 per cent, monocytes 10 per cent. The sternal marrow aspiration was repeated and it revealed over 90 per cent lymphocytes and lymphoblasts in a very cellular marrow (fig. 3). On 5-3-46 he was given his first injection of crude myelokentric acid. This was a chloroform extract of hydrolyzed urine made up in alkaline water solution at a pH of 7.5 (1 cc. was equal to 1,000 cc. of urine). At first he was given 1 cc. daily. He had averaged 1 cc. daily throughout the entire treatment period up to August 3 although in the months of June and July the material was given two to four days apart in 1 to 4 cc. injection doses. At first he had a fever of 101° to 104° F. daily and because of a cough and rhinitis he was given penicillin by
injection for two weeks. The erythrocyte count was maintained by blood transfusion. The first month it was necessary to give a blood transfusion every four or five days, but after June 1 the intervals between transfusions were ten days to two weeks. The leukocyte count dropped slowly until it reached a low point of 1,400. As the total count fell the lymphoblasts dropped steadily in percentage and actual numbers. Gradually the leukocyte count began to return to normal levels, and as it did normal lymphocytes and polymorphonuclear leukocytes made up the greater part of the differential count. On June 22 the erythrocyte count was 2,600,000, hemoglobin 54 per cent, the leukocyte count was 3,500, and the platelet count was 138,000. The differential count was polymorphonuclear neutrophiles 48 per cent, lymphocytes 50 per cent, lymphoblasts 2 per cent. Another bone marrow aspiration was done on June 18, and it revealed a very hyperactive marrow with about one-third of the cells myeloid in character including red cell and platelet formation (fig. 4). The liver, spleen, and lymph nodes all were reduced somewhat in size. He became more active and his appetite was very good. June 28 he was discharged to be observed outside of the hospital. From then until this writing, 8-3-46, he has remained in partial remission.

Case 9. A. C., a 30 year old white man, had been ill for about ten weeks when he entered Jefferson Hospital 1-16-40. He had had night sweats, some fever, had lost 17 or 18 pounds in weight, and had noted four weeks before entry that the lymph nodes in his neck were swollen. Ten days before coming to the hospital his vision was blurred in the right eye. On examination there was a hemorrhage in the retina and evidence of recent bleeding from both nostrils; there was generalized enlargement of the peripheral lymph nodes, and the spleen was enlarged about 1 centimeters below the costal margin. The hemoglobin was 69 per cent, erythrocyte count was 3,000,000, and the leukocyte count was 26,000. The platelet count was 70,000 and the differential count was polymorphonuclear neutrophiles 12 per cent, lymphocytes 74 per cent, meyelocytes 10 per cent, lymphoblasts 4 per cent. A bone marrow aspiration revealed a cellular marrow made up largely of lymphoblasts. He was given a total of 1,000 r of x-ray over neck, chest, and groins. His temperature was 102° F. to 104° F. daily. He developed oozing of blood from nose and gums and many petechiae over the entire body. The leukocyte count fell to 5,000 1-18-40 but rapidly rose to 110,000 the day before he died. He died 1-16-40 and a necropsy was performed.
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Case 10. R. S., a 33 year old white boy, entered Jefferson Hospital 6-17-41 because of pallor and a distended abdomen. He was well until 3-1-40, at which time he had had a “cold.” Shortly after that, because of pallor and distention of the abdomen, he was taken to a hospital where the diagnosis of leukemia was made. Prior to admission to Jefferson Hospital he had had several transfusions. His erythrocyte count was maintained, with difficulty, at around 3,000,000. His leukocyte count varied from 15,000 to 35,000 and the cells in the peripheral blood were all termed lymphocytes.

In Jefferson Hospital it was found that all of the peripheral lymph nodes were moderately enlarged. The abdomen was found to be large because of the size of the spleen and liver. The erythrocyte count was 1,200,000, hemoglobin 34 per cent, leukocyte count was 107,000 and the platelet count was 44,000. The differential count was lymphocytes 65 per cent, lymphoblasts 35 per cent. He was given five transfusions, and the last two days of his life he was given two injections of the inactive neutral fraction of extract from feces. The erythrocyte count was 1,400,000, hemoglobin 29 per cent, and the leukocyte count was 5,000 the day of death with no change in the differential count. The day of death it was found that he had an abscess of his right buttock. He died 6-19-41; a necropsy was performed.

Case 11. H. S., a 16 year old boy, entered Jefferson Hospital 4-14-45 because of pains in the muscles of arms and legs, loss of weight, and fever for a period of four months. He had been in another hospital in January 1945 and was thought to have rheumatic fever. At that time it was found that he had anemia and had a fever of 102° to 103° F. daily. When he entered Jefferson Hospital it was obvious that he had lost weight. At this time the spleen and liver were palpable, there was slight enlargement of the inguinal lymph nodes, but other lymph nodes were not enlarged. The sternum and the bones of the legs were tender to pressure.

X-ray examination of the chest showed nothing abnormal, but examination of the legs showed an elevation of the periosteum of each fibula, more on the left than on the right. A sternal marrow aspiration revealed a very hyperplastic marrow, the cells of which were preponderantly lymphoblasts. At this time his peripheral blood was not particularly abnormal. On 4-19-45 the erythrocyte count was 3,700,000 with

Fig. 4. Material from Bone Marrow Aspiration after 6 Weeks of Treatment, Case 8.
Wright’s Stain X 900

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a hemoglobin of 69 per cent. The leukocyte count was 7,900 with a differential count of polymorphonuclear neutrophiles 64 per cent, eosinophiles 1 per cent, basophiles 1 per cent, lymphocytes 27 per cent, monocytes 6 per cent, lymphoblasts 1 per cent. A biopsy of the fibular marrow revealed a lymphoid reaction with infiltration of lymphoid cells into the cortical bone.

The peripheral blood gradually changed so that on 5-18-45 in 15,000 leukocytes 42 per cent lymphoblasts were present. He became more anemic and it was necessary to give him blood transfusions. He had also an infection of his right eye which was controlled with penicillin. On 6-5-45 his leukocyte count was 24,000 and of these 77 per cent were lymphoblasts. Late in the disease he bled from the urinary tract, bowels, and nose. The day before death the leukocyte count was 108,000 with 81 per cent lymphoblasts. He died 6-9-45 and a necropsy was performed.

Case 12. S. W., an 8 month old colored girl, one of twins, entered Jefferson Hospital 4-17-45 because of swelling of the eyelids, irritability, and anorexia. There was a generalized lymphadenopathy, the eyelids were swollen, the mucous membranes were pale, and the liver enlarged. She had been ill for about two weeks. The erythrocyte count was 1,700,000 with a hemoglobin of 11 per cent, the leukocyte count was 38,000, and the differential count was polymorphonuclear neutrophiles 4 per cent, lymphocytes 4 per cent, and lymphoblasts 97 per cent. Her platelet count was 4,000. The leukocyte count fell in two days to 1,000. Transfusion of blood was given but she died 4-19-45 and a necropsy was performed.

**PATHOLOGY**

Grossly there were no clear-cut variations between the treated and untreated cases. Petechiae and hemorrhages were present in the skin of 2 of the controls and in 3 of the treated, and in the pericardium of 1 of the former and of 3 of the latter. In both groups there was generalized enlargement of the lymph nodes to a maximum of 2.5 cm. in diameter. Making an allowance for the difference in ages, the spleens of the untreated children (weighing 170 Gm. in case 9 and 90 Gm. in case 12) were definitely larger than were those of the treated ones (weighing 120 Gm. in case 5, 50 Gm. in case 4, 120 Gm. in case 1, and 90 Gm. in case 6, and 150 Gm. in case 7). All livers were enlarged but they showed no appreciable change in size and appearance in the two groups. The involvement of the kidneys was more extensive in control cases 9, 11, and 12 (one kidney in each weighing 320 Gm., 670 Gm., and 90 Gm. respectively) than it was in the treated cases 1, 4, 5, 6, and 7 (whose corresponding weights were 130 Gm., 150 Gm., 110 Gm., 55 Gm., and 90 Gm. respectively). The cortices in each were swollen and pale brown and exhibited irregular petechiae and larger blotchy areas of erythrocytic extravasation. Hemorrhages in the lungs, prominence of the lymphoid patches in the intestines, and the appearance of the bone marrow were the same in both groups.

**Microscopic:** Histologic sections of all organs were stained with hematoxylin and eosin and in addition sections of the lymph nodes, liver, spleen, and bone marrow were stained with Foote's reticulum stain, Giemsa's stain, and Masson's trichrome stain.

**Lymph Nodes:** In both the control and treated cases the normal architecture was almost completely effaced and the capsules were infiltrated with leukemic cells. In the controls there was a diffuse and dense or moderate infiltration with lymphoblasts and lymphocytes and almost no pleomorphism of cells (fig. 5). In the background there were sparse reticulum cells, occasional polymorphonuclear leukocytes, and no phagocytes. In case 12 the vessels were quite prominent and there was a slight increase of perivascular connective tissue but in none of the cases was there reticulum hyperplasia.
In contrast, the lymph nodes of the treated cases disclosed (1) an increase in vascularity with sometimes a surrounding zone of necrosis, (2) reticulum hyperplasia, and (3) an unmistakable pleomorphism of cells. The vessels were thick-walled capillaries often distended with erythrocytes. Their outlines were usually distinct but sometimes they merged directly with a surrounding zone of necrosis (fig. 6). The reticulum cells were either diffusely increased or formed conspicuous...
bands of cells radiating peripherally from the medulla (figs. 7, 8, and 9). The cells were large, polygonal or irregular in shape, and contained round evenly stained nuclei and an abundant amount of pink cytoplasm with processes often attached to the underlying reticulum. While the infiltrating cells were mostly lymphocytes and lymphoblasts, the pleomorphism was sometimes so marked and of such a nature as to suggest a more than striking resemblance to Hodgkin's disease (fig. 10). The most conspicuous elements perhaps were very irregularly shaped cells of an over-cell size equal to that of lymphocytes or lymphoblasts. They contained almost
imperceptible cytoplasm and darkly stained nuclei, and were undoubtedly distorted lymphocytoid cells. In addition to these cells there were scattered phagocytes, polymorphonuclear leukocytes, eosinophiles, plasma cells, and large mononuclear or multinuclear cells resembling Sternberg-Reed cells. Some of the nodes also disclosed a diffuse, early fibrosis. Sections of the thymus from case 6 showed a reticulum cell hyperplasia and a pleomorphism of cells similar to that seen in the nodes of the same case.

Liver: The leukemic infiltrates in the livers of the control cases were prominent...
throughout the portal radicles and very sparse between the liver cords (fig. 11). In cases 9, 10, and 11 all the extraneous cells were lymphoblasts or lymphocytes, whereas in case 12 there were also a few distorted cells in the portal radicles. Con-

![Fig. 11. Section of a Liver from an Untreated Case Showing Massive Portal Infiltration with Lymphoid Cells. Hematoxylin and Eosin X 100](image1)

![Fig. 12. Section of a Liver from a Treated Case Showing a Portal Radicle from Which the Leukemic Cells Have Been Almost Completely Washed Away Leaving a Naked Scanty Underlying Reticulum. Hematoxylin and Eosin X 100](image2)

nective tissue cells were slightly increased in the latter location in case 12 but were not evident in cases 9, 10, and 11, and Kupffer's cells were difficult to demonstrate in any of the controls. The distribution of the leukemic cells in the livers from the
treated cases was essentially the same as that in those from the controls. The former, however, differed from the latter in that there was (1) a definite pleomorphism of cells similar to that already described in the lymph nodes, (2) a hyperplasia of reticulum cells, (3) an increase in reticulum and a corresponding depletion of lymphoid cells (figs. 12, 13, and 14), and (4) a swelling, bulging, and what even appeared to be a detachment of some of the Kupffer’s cells into the sinusoidal lumens (fig. 15). Except for some increase of fat droplets in the liver cells, the hepatic structure was otherwise unchanged.
**Spleen:** Sections of the spleens from the controls showed a few distorted follicles remaining in case 12 and a complete effacement of the normal architecture in cases 9, 10, and 11 (fig. 16). In the latter the cells were almost all of the lymphocytic type, but in case 12 there were also a few phagocytes and occasional polymorpho-

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**Fig. 15. Section of a Liver from a Treated Case Showing Very Prominent Kupffer’s Cells, Some of Which Appear to be Extruding into the Lumen. Hematoxylin and Eosin X 400**

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**Fig. 16. Section of a Spleen from an Untreated Case Showing a Complete Effacement of the Normal Architecture and a Diffuse Infiltration with Lymphoid Cells. Hematoxylin and Eosin X 100**

...nuclear leukocytes and eosinophiles. In this case the sinuses and reticulum were discernible, although not hyperplastic, while in cases 9 and 10 they were inconspicuous. Sections of the spleens from the treated cases showed the same topographical changes as did those from the untreated ones. As in the other organs they
differed from the latter in that there was (1) a focal or diffuse increase in reticulum (figs. 17 and 18), (2) a prominence of the sinusoids, and (3) a marked pleomorphism of cells. In case 6 some of the foci of reticulum hyperplasia disclosed early necrosis but in the remaining cases such degenerative changes were not encountered. In case

1, whose spleen was removed before treatment, there was no increase in reticulum and no such pleomorphism of cells as was seen in the spleens of treated cases. In all treated cases although most of the infiltrating cells were lymphoblasts and lymphocytes there were also varying numbers of phagocytes, reticulum cells, monocytes,
plasma cells, polymorphonuclear leukocytes, eosinophiles, and large mononuclear or binuclear cells resembling Sternberg-Reed cells (fig. 19).

Bone Marrow: Sections of sternal and vertebral bone marrow were studied histologically. In the control cases it was diffusely involved, showing a moderate or dense infiltration with leukemic cells (fig. 10). These composed from 75 per cent to 90 per cent of all the marrow elements with the remaining constituents consisting of megakaryocytes and cells of the erythrocytic and myelocytic series. There was
osteosclerosis in case 10 but in none of the cases was there reticulum cell hyperplasia or fibrosis. Sections of the marrow from the treated cases also showed a diffuse involvement but, in contrast to those of the control cases, it was less cellular and distinctly more "washed out" (fig. 21). About one-half of the infiltrating cells

were lymphoblasts and lymphocytes whereas the remainder was composed of reticulum cells, large primitive cells resembling Sternberg-Reed cells, plasma cells, few eosinophiles, polymorphonuclear leukocytes, and other unidentified cells (fig. 22). Throughout the sections there was a diffuse or focal increase of reticulum
to which processes of the reticulum cells were often attached (figs. 2.3 and 2.4). All sections showed almost a complete absence of megakaryocytes.

**Kidney:** The leukemic infiltrates in the kidneys were similar in distribution in both the control and treated cases. They were confined to the interstitial tissue of the tubules and around the glomeruli, and varied from a few foci to severe infiltrations. In the untreated cases the cells were entirely of the lymphocytic type but in the treated ones there were also distorted cells, plasma cells, monocytes, occasional eosinophiles, and polymorphonuclear leukocytes. Erythrocytic extravasation occurred with increasing frequency as the disease progressed.

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**Fig. 2.3.** Section of bone marrow from an untreated case showing a paucity of reticulum. 
FooTe's Reticulum Stain  X 100

**Fig. 2.4.** Section of bone marrow from a treated case showing a marked increase in reticulum. 
FooTe's Reticulum Stain  X 100
asation, although present in both groups, was much more severe in the treated cases.

Other Organs: In both the control and treated cases small foci of leukemic cells were found in the adrenals, lungs, heart, pancreas, and skin. Except for some of the pleomorphism already referred to, these foci were similar in both groups. There was a variety of cells in greatly hyperplastic lymph follicles of the intestine in both the treated and untreated cases and in each there was ulceration of the overlying epithelium. Congestion, edema, and hemorrhages were found with equal frequency and severity in the lungs of both groups of cases.

RECAPITULATION OF CLINICAL AND PATHOLOGICAL MATERIAL

The clinical part of this paper is presented in order that it may be seen that a trend toward normal blood levels was initiated in each of the treated cases. This was especially true in cases 1, 2, 4, and 8. To a lesser degree it was apparent in cases 3, 5, and 6, while in case 7 the trend was very slight.

In each case except case 1 there was a marked drop in total leukocyte count twelve days to six weeks following the first dose of crude myelokentric acid. The leukocyte counts of cases 2 and 4 reached levels under 1,000; those of cases 6 and 8 were reduced to under 2,000 cells. In case 1 the level of the leukocytes was under 2,000 when treatment was started. Case 5 reached a low count of 3,000 and case 3 a low count of 4,500. After the lowest count was reached in each case, with the exception of cases 3 and 7, the subsequent rise was accompanied by normal elements in the hemogram. As the leukocyte counts began to rise young erythrocytes and increased numbers of platelets were found in the peripheral blood. The bone marrow aspirations that were obtained after the leukocyte counts began to rise and normal elements had appeared in the peripheral blood of cases 1, 2, 4, and 8 revealed a regeneration of myeloid elements and a diminution of lymphoid cells as compared with the aspirations obtained prior to treatment. Five of the 8 cases had remissions so marked that transfusions were unnecessary for periods of from three weeks to two months. In cases 1, 2, 4, 5, and 6 during these periods the erythrocyte levels were maintained at or above 3,000,000 cells. Before treatment and throughout the first five weeks of treatment case 8 required transfusion not less than once a week and frequently every four to five days. As treatment progressed this case required transfusion only every ten days to two weeks. The size of lymph nodes, spleen, and liver was reduced in each case that received this treatment, although case 3 showed some fluctuation in the size of the lymph nodes irrespective of treatment.

The leukocyte count of case 9 fell from 26,000 to 5,000 in two weeks of observation, but again increased to 110,000 before death and there was no change in the organ pathology. The leukocyte count of case 10 fell from 107,000 to 5,000 in twelve days, but there was no change in the size of the spleen or liver or of the lymph nodes, and necropsy material showed no alteration from the usual leukemic process. A change from normal leukocyte levels with normal differential values to leukemic levels with large numbers of abnormal cells occurred in case 11 in a five week period, and of course the necropsy material was typical of lymphoid leukemia. The leukocyte level of case 12 dropped from 38,000 to 5,000 in two days, again without change in organ pathology.
The relationship of infection to the partial remissions reported here must be considered, because cases 2, 4, 5, and 6 each had severe infections. Cases 1, 3, 7, and 8, however, did not have severe infections and the remissions and necropsy material were much the same whether or not infection had been encountered. Aside from these facts 2 of the control cases had infection which did not alter the course or organ pathology in these cases. Others also have remarked on the coincidence of infection in the leukemias of childhood, but in such reports it is rare to find a change in the pathology of the disease from the action of the infective agent. Case 5 (a treated case) and case 10 (a control) were each given small doses of x-ray. It seems unlikely that the alteration in organ pathology could be accounted for by the action of x-ray in case 5.

The length of life of all cases is shown in table 1. In the treated cases we have used the length of life from the start of treatment to death, and for the untreated cases from the start of our observations to death. This is too small a series from which to draw any conclusions, but the table is given because of the striking difference between the two groups.

<table>
<thead>
<tr>
<th>TREATED</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1—6½ months</td>
<td>Case 9—11 days</td>
</tr>
<tr>
<td>Case 2—8 months</td>
<td>Case 10—1 month</td>
</tr>
<tr>
<td>Case 3—6 months</td>
<td>Case 11—2 months</td>
</tr>
<tr>
<td>Case 4—4 months</td>
<td>Case 12—2 days</td>
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<tr>
<td>Case 5—2½ months</td>
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</tr>
<tr>
<td>Case 6—1 months</td>
<td></td>
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<tr>
<td>Case 7—3 weeks</td>
<td></td>
</tr>
<tr>
<td>Case 8—6½ months (still living)</td>
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</tr>
</tbody>
</table>

We believe that we have induced partial remissions in these 8 cases thirteen times. This number of remissions is obtained by adding the very definite changes that occurred in the blood picture and bone marrow and in the general condition of the patients to the changes that occurred toward the end of life in cases 1, 4, and 7. We believe that these latter were consistent with the necropsy findings.

The remissions were more complete in cases 1, 2, 4, and 8 than in the other cases. The necropsy material of case 7, however, represented a greater change from the usual leukemic process than did material from the other 4 in the treated necropsy group. It is interesting in this connection that to cases 1, 2, 7, and 8 liver extract (anti-anemia factor), 1 to 3 units, was given with each dose of crude myelokentric acid. A relationship between the action of the two substances might be suggested but further work is needed to be certain of this.

It must be remembered that all the material used was crude and because of the variations in its source great variations in potency occurred from one lot to another. Cases 5 and 6 might have gone further into remission except that at a crucial point in each case, because of lack of urine, it was necessary to reduce the dose of the extract. Then, too, patients may build up an increased tolerance to the material and need more of it the longer they are treated. It should be pointed out that 2 patients,
cases 1 and 2, were given inactive fractions of urine extracts for adequate periods of
time with no effect on the blood picture or improvement in general condition.

The histopathologic changes in the various organs of the treated cases are in
keeping with the clinical picture. That the injected material had an effect upon the
leukemic process was indicated in several ways. The earliest manifestation, per-
haps, was a change in the morphologic appearance of the lymphocytic cells from
the regular, round, evenly staining forms to very irregular, distorted, and pyknotic
cells. This was most apparent in those locations where the leukemic infiltrations
were most severe. Although the bone marrow was diffusely involved in all the
treated cases, there was a decrease of cellularity to a degree consistent with a diag-
nosis of hypoplasia. A later result, which suggested healing, was indicated by an
increase of reticulum and fibrous tissue with a corresponding decrease of leukemic
cells. This was particularly evident in the liver from cases 1 and 7. Finally, the effect
of treatment was manifested in the marked pleomorphism evoked especially in the
lymph nodes, spleen, and bone marrow, and in the reticulum cell hyperplasia best
exemplified in the lymph nodes and spleen.

The injections of organ extracts have caused partial remissions in acute leukemia
(Cooke, 1938) but no such change in the pathologic morphology.

DISCUSSION

Myelokentric acid is a noncarbinol acid that is found in the urine of patients with
acute or chronic myeloid leukemia, chronic lymphoid leukemia, monocytic leu-
kemia, Hodgkin’s disease, and in liver lipids. Lymphokentric acid is an hydroxy-
acid that is found in the urine of patients with acute or chronic lymphoid leukemia,
lymphosarcoma, chronic myeloid leukemia, monocytic leukemia, Hodgkin’s dis-
ease, and in liver lipids. These two acids are chemically interconvertible: i.e., by
reduction myelokentric acid may be converted from a noncarbinol to an hydroxy-
acid and the end product is biologically active as a stimulator of lymphopoiesis,
and the reverse is also true: i.e., by oxidation, lymphokentric acid may be converted
from an hydroxyacid to a noncarbinol acid and the end product is biologically
active as a stimulator of myelopoiesis.

We believe that these substances are of fundamental importance in the abnormal
processes of blood cell production in the leukemias. It is also possible that they
constitute the balance mechanism in normal blood cell proliferation and matura-
tion. We do not believe that they are the causative agents for leukemia.

Leukemia in the human individual may exist without any known precursor but
frequently it occurs following a precipitating incident or set of incidents. These
may be exposure to x-ray or radium, contact with or exposure to benzol or its
derivatives, trauma—either physical or mental—the use of arsenical or sulfonamide
drugs, infection of various types as well as other factors and agents. These incidents
or agents are not the causes of leukemia per se but each may act to upset the normal
balance of blood cell formation so that leukemia results, and it then continues till
the death of the individual even if the inciting agent has been removed.

It is our contention that the leukemias represent a group of metabolic disorders in
which the various types are not well separated on a physiologic basis. These metabolic disorders may be expressions of the excesses or deficiencies of myelokentric and lymphokentric acids and/or imbalances in the normal relationship of the lymphoid and myeloid systems.

Ziegler was the first to propose that myeloid and lymphoid cells and tissues were balanced and interrelated in their activities. It has been apparent almost from the earliest classification of blood cells that when the lymphoid system was hypertrophic the myeloid system was diminished in activity and vice versa. Evidence of this type of interrelationship of the two hematopoietic systems occurs in the myeloid response to various bacterial infections and the lymphoid response to certain filter-passing viral infections. It is also evident in certain of the metabolic diseases, as, for example, reduction in the hormones from the cortex of the adrenal is accompanied by myeloid atrophy and lymphoid hypertrophy while in Cushing's syndrome the reverse may be found.

Each of the three large groups of leukemia seem to represent exaggerations of this process. In chronic myeloid leukemia, for instance, hyperactivity of the bone marrow elements occurs. This represents not only an increased production of cells but, along with the increased number of cells, there is also an increase in maturation. Throughout the greater part of the disease there is not only an overabundance of cells but an overabundance of cells that are apparently normal in morphology and biologic reactions. Throughout the greater part of the disease the lymphoid system appears normal and at least normal numbers of lymphocytes appear in the peripheral blood. Toward the end of the disease the lymphoid system is frequently replaced by myeloid cells and the lymphoid cells disappear from the peripheral blood, and at this time, to a large extent, the maturation of the myeloid cells ceases. This is termed the blastic phase of chronic myeloid leukemia and is comparable, if not identical, with the acute form.

We have suggested previously that myelokentric acid and lymphokentric acid are mutually reciprocal in action and that myelokentric acid stimulates myelopoiesis without maturation. We contend that the maturation of myeloid cells is brought about by the action of lymphokentric acid which inhibits the proliferation of myeloid cells and hence allows them to mature. In chronic myeloid leukemia throughout the greater part of the disease there is an excess of myelokentric acid and at least a normal amount of lymphokentric acid. Such a mechanism brings about excessive proliferation and maturation of myeloid cells and normal production of lymphoid cells. As the lymphokentric acid becomes exhausted maturation of myeloid cells ceases, and this coincides with the disappearance of the lymphoid cells from the blood and tissues. The mechanism involved in acute myeloid leukemia is consistent with a lack of lymphokentric acid and a normal or increased value of myelokentric acid. Some acute myeloid leukemias show slight maturation of myelocytes and probably have available small amounts of lymphokentric acid, but in each one there is a deficiency of lymphokentric acid and lymphopoiesis.

A similar picture can be drawn for a chronic lymphoid leukemia with its increased proliferation and maturation. In this disease if the myeloid system becomes
exhausted and the bone marrow is replaced with lymphoid elements less and less maturation of the lymphoid cells will occur and an acute phase will result. This is encountered less frequently than the similar phase of chronic myeloid leukemia.

Again, we have suggested previously that lymphokentric acid brings about lymphoid proliferation without maturation. The maturation of lymphoid cells is brought about by the action of myelokentric acid which inhibits the proliferation of lymphoid cells and hence allows them to mature. In chronic lymphoid leukemia there is an excess of lymphokentric acid and at least a normal amount of myelokentric acid. An excessive proliferation and maturation of lymphoid cells and a normal production of myeloid cells occurs because of such a mechanism. When the myelokentric acid becomes exhausted maturation of lymphoid cells ceases and little or no production of myeloid cells occurs. The mechanism involved in acute lymphoid leukemia is consistent with a lack of myelokentric acid and a normal or increased amount of lymphokentric acid so that lymphopoiesis goes on in a proliferative but unmaturative manner without myelopoiesis.

It is more difficult to explain the monocytic leukemias on this basis. We have reported previously, however, that extracts of the urine from patients with monocytic leukemia contained excessive amounts of both myelokentric acid and lymphokentric acid. Hypothetically the overstimulation of both lymphoid and myeloid systems at the same time might result in a monocytic proliferation accompanied by some pleomorphism and either much or little maturation of the cells involved.

SUMMARY

Eight cases of blastic lymphoid leukemia have been treated with myelokentric acid in crude form, because hypothetically in blastic lymphoid leukemia there is a deficiency of this material. The crude myelokentric acid was used because it was more easily obtained than partially purified material. Purification of biologically active materials by methods of extraction and precipitation necessarily results in a considerable loss of material. Thirteen partial remissions occurred following the administration of crude myelokentric acid. Seven of the 8 patients have died, and 5 necropsies were performed.

The necropsy material adds further weight to the belief that the remissions were induced by the myelokentric acid in that in all 5 necropsies there was a definite alteration in the histologic morphology as contrasted with the findings in the necropsies of the controls.

It seems inadvisable, however, to treat a large number of patients with this material because it is crude, it is relatively unavailable, and no standard dose has yet been devised.

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REFERENCES

F. R. MILLER, P. A. HERBUT AND H. W. JONES

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6 Unpublished data.


THE TREATMENT OF LYMPHOBLASTIC LEUKEMIA WITH CRUDE MYELOKENTRIC ACID

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