MEASURES introduced for the treatment of leukemia have two points of interest. In the first place, any treatment which may mitigate the symptoms and prolong the useful life of persons suffering with a fatal disease of unknown etiology possesses intrinsic merit. In the second, the therapeutic trial of agents which have a demonstrable effect on the growth of leukemic cells is justifiable because of the contributions which may thereby be made to the knowledge of the pathologic physiology of the disease.

In 1944, Flory1 reviewed the status of those forms of therapy for leukemia which up to that time had been used with varying degrees of benefit. Since then, Paterson and her associates2 have presented evidence that urethane (ethyl carbamate) is capable of causing improvement, especially in patients with chronic myelogenous leukemia, and Goodman and others3 have described favorable results obtained with “nitrogen mustard” therapy in some patients with leukemia. The purpose of this communication is to present data which indicate that para-aminobenzoic acid (as sodium para-aminobenzoate) is capable of causing certain definite effects in chronic myelogenous leukemia.

Since para-aminobenzoic acid (PABA) is generally considered to be a member of the B-complex group of vitamins4,5 and is known to be a normal constituent of many food substances,4 it appears to us that the following observations of its effects in leukemia are of sufficient significance to warrant publication at this time.

Para-aminobenzoic acid has been successfully employed in the treatment of the rickettsial diseases of man.6,7 It was apparent during the earlier studies of the clinical effects of PABA in louse-borne typhus fever that PABA inhibited the growth of rickettsiae indirectly, that is, by influencing the metabolism of the parasitized cells in some manner.6 During these studies, it occurred to one of us (C.Z.) that cells of disordered metabolic function, that is, neoplastic cells, might not be able to adapt to a substrate containing PABA in high concentration. In view of the apparent non-toxicity of large doses of PABA in typhus patients, it was judged safe to test this hypothesis in patients with leukemia.

The present report deals with the results obtained in the study of 10 patients to whom PABA was administered. Five of these subjects had chronic myelogenous leukemia, three had subacute myelogenous leukemia, of whom two were subclassified as erythroleukemia, and two had chronic lymphatic leukemia.

For administration to the patients, para-aminobenzoic acid (PABA)** was placed in solution by conversion to sodium para-aminobenzoate (NaPAB) with sodium...
bicarbonate. The final volume was adjusted to make a 10 per cent solution of NaPAB which was administered orally to the patients in 2.0 cc. to 40 cc. doses (2.0 Gm. to 4.0 Gm.) every two hours, day and night. The solution was taken most readily in a small amount of fruit juice or ginger-ale. The schedule of therapy employed here is similar to that used in the treatment of certain of the rickettsial diseases.\textsuperscript{6,7} The two-hourly schedule is required to maintain a desired blood level since this compound is rapidly excreted in the urine. Purely on an empiric basis, an attempt was made to keep the blood level of NaPAB between 10 and 30 milligrams per cent, although this level was frequently exceeded without any apparent ill effect. In some instances the dosage schedule was modified for patients who continued to take NaPAB at home. They were allowed to double the doses and the intervals between them during the night in order to obtain more rest.

### Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Initial white count</th>
<th>Lowest white count</th>
<th>No. days treatment in lowest count</th>
<th>Total Gm. NaPAB to lowest count</th>
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<tr>
<td>1. F. G.</td>
<td>Chronic myelogenous leukemia</td>
<td>427,150</td>
<td>15,150</td>
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<td>2. K. P.</td>
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<td>230,500</td>
<td>38,000</td>
<td>28</td>
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<td>3. E. N.</td>
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<td>155,500</td>
<td>24,000</td>
<td>28</td>
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<td>4. C. W.</td>
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<td>140,000</td>
<td>20,500</td>
<td>22</td>
<td>998</td>
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<td>5. R. M.</td>
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<td>38,250</td>
<td>15</td>
<td>700</td>
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<td>6. L. B.</td>
<td>Subacute erythroleukemia</td>
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<td>13,000</td>
<td>15</td>
<td>249</td>
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<td>7. A. C.</td>
<td></td>
<td>8,000</td>
<td>2,500</td>
<td>15</td>
<td>580</td>
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<tr>
<td>8. L. D.</td>
<td>Subacute myelogenous leukemia</td>
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<td>1,500</td>
<td>36</td>
<td>1182</td>
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<td>9. C. K.</td>
<td>Lymphatic leukemia</td>
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<td>101,750</td>
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<td>566</td>
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<tr>
<td>10. R. W.</td>
<td></td>
<td>440,000</td>
<td>352,500</td>
<td>18</td>
<td>518</td>
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</tbody>
</table>

### Case Reports (Table 1)

**Case 1.** F. G., a 45 year old white salesman, was admitted to the Simpson Memorial Institute on October 31, 1946. He had been well until May, 1946, when he noted loss of weight and progressive ease of fatigue. Symptoms of hypermetabolism were also present.

Physical examination revealed obesity and slight pallor. Several ecchymoses were present over the abdomen and lower extremities. There were no palpable lymph nodes. The liver descended 5 cm. below the right costal margin, and the spleen was greatly enlarged, extending 4 cm. to the right of the umbilicus and down two-thirds of the distance between the umbilicus and symphysis pubis.

On admission the hemoglobin was 11.0 grams per 100 cc., red blood cells 3,600,000 per cubic millimeter, and white blood cells 471,500 per cubic millimeter. The red cell packed volume was 33 per cent, and the white cell packed volume was 2.0 per cent. The differential count revealed myeloblasts 0.5 per cent, promyelocytes 1 per cent, myelocytes 2.0 per cent, metamyelocytes 2.1 per cent, band neutrophils 13.5 per cent, segmented neutrophils 35.5 per cent, eosinophils 3 per cent, basophils 1.5 per cent, lymphocytes 0.5 per cent, and hemophiliocytes 0.5 per cent. Bone marrow findings were compatible with the diagnosis of chronic myelogenous leukemia. Urine analysis was negative. Fasting blood sugar was 50 milligrams per 100 cc., the blood cholesterol was 132 milligrams per 100 cc., and the basal metabolic rate was plus 18 per cent.

On November 4, NaPAB was started 2 Gm. every two hours, and increased to 4 Gm. every two hours four days later. The patient continued to receive NaPAB for twenty-seven days, taking a total of 1,096 Gm. During this time his leukocyte count fell from 427,150 to 15,150 per cu. mm. The red cell packed volume rose from 31.0 per cent to 35.5 per cent, while that of the white cells decreased from 17.0 per cent...
to 1.5 per cent. The hemoglobin level increased from 10.8 Gm. to 11.1 Gm. per 100 cc. Throughout the period of medication, there was constant glycosuria of 2 to 3 plus. The blood levels of NaPAB reached 37.2 mg. per cent. The patient's spleen decreased in size during the period of therapy, and for some time after its discontinuance. On December 9, when the patient had received no NaPAB for the preceding nine days, his hemoglobin was 12.8 Gm., red cell packed volume 41.0 per cent, white cell layer 2 per cent, leukocyte count 33,050 per cu. mm., with differential values essentially as before.

The patient was seen again on December 18, 1946. The spleen had enlarged considerably from the previous examination, and the leukocytes numbered 167,450 per cu. mm. with 9 per cent myeloblasts.

Three weeks later the leukocytes had increased to 335,000 per cu. mm. and there was further enlargement of the spleen. Differential count showed 11 per cent blast cells. Platelets were decreased. The hemoglobin was 9.6 Gm. The basal metabolic rate was plus 67 per cent. The patient was admitted for further treatment and was given 4 Gm. NaPAB every two hours, day and night. After eighteen days, the leukocytes numbered 141,000, and the hemoglobin was 8.0 Gm. The basal metabolic rate at this time was plus 50 per cent, and the patient had gained a few pounds in weight. He was discharged to continue taking NaPAB, 16 Gm. daily at home. At the end of two weeks, the leukocyte count fell to 58,300 per cu. mm., and the red cell values remained stationary. At this time he had 54.5 per cent blast cells. Thereafter, his leukocytes began to increase despite the continued administration of NaPAB. On February 25, after forty-two days of continuous medication, the white count was 104,750 per cu. mm. with 59 per cent blast forms. NaPAB was discontinued and the patient felt fairly well for two or three days, but then began to lose ground rapidly. He was readmitted on March 1, 1947. He appeared extremely ill, and was dyspneic, weak, and very apprehensive. The spleen was greatly enlarged, and the leukocytes numbered 344,000 per cu. mm. with 83 per cent blast forms. The patient became increasingly dyspneic and developed signs of circulatory collapse. Blood transfusion and oxygen were administered, but he died on the following day. Permission for autopsy was not obtained.

This patient received two courses of NaPAB over twenty-seven and forty-two days, respectively. He was given a total of 1,538 Gm. of the drug. Glycosuria was noted during both courses of NaPAB administration. Chart 1 illustrates the changes in leukocyte counts and hematocrit values during the period of observation.
Case 2. K. P. (Chart 2). This 69 year old white man first experienced symptoms of exertional dyspnea, weakness, and ease of fatigue in October, 1945. In November, 1945, he was admitted to the University Hospital and the diagnosis of chronic myelogenous leukemia was made. He received a course of total body x-ray irradiation with excellent symptomatic improvement. However, weakness and fatigue reappeared in April, 1946, and he was given more irradiation therapy and several transfusions during May, 1946. He returned on October 1, 1946, and was admitted to the Simpson Memorial Institute. The patient was pale and appeared to have lost much weight. The liver was palpable 3 cm. below the right costal margin, and the spleen was greatly enlarged, descending 3 cm. below the umbilicus.

On admission the hemoglobin was 7.9 Gm. per 100 cc., erythrocytes 1,600,000, and leukocytes 230,000 per cu. mm. The red blood cell packed volume was 23 per cent, and the white cell packed volume was 10 per cent. The differential count was as follows: myeloblasts 6 per cent, promyelocytes 3 per cent, myelocytes 16 per cent, metamyelocytes 7 per cent, band neutrophils 2.6 per cent, segmented forms 11 per cent, basophils 12 per cent, and eosinophils 8 per cent. The platelets were slightly increased. The fasting blood sugar level was 75 mg. per 100 cc. The patient was given 24 Gm. of NaPAB daily from October 2 to October 29 when his leukocytes numbered 38,000 per cu. mm. He was discharged on October 31 and was not seen again until January 7, 1947.

The spleen now reached a point 6 cm. below the umbilicus, and the liver extended 4 cm. below the right costal margin. The hemoglobin was 7.5 Gm., the red cells 1,400,000, and the leukocytes 154,950 per cu. mm. The red cell packed volume was 23 per cent, and the white cell packed volume was 9 per cent. The differential count revealed myeloblasts 8 per cent, promyelocytes 5.5 per cent, myelocytes 17.5 per cent, metamyelocytes 21.0 per cent, band neutrophils 17.5 per cent, segmented neutrophils 13 per cent, basophils 11 per cent, eosinophils 5.5 per cent, lymphocytes 0.5 per cent, and hemophistiocytes 0.5 per cent. The platelets were increased. Beginning on January 15, the patient received 48 Gm. NaPAB daily for three days and 24 Gm. daily thereafter. The dosage was decreased because the blood levels attained on 48 Gm., a day ranged from 56 mg. per cent to more than 70 mg. per cent. By February 1, the white cell count had fallen to 60,000 per cu. mm. and the spleen was slightly smaller and considerably softer than on admission. There was a gain of four pounds. However, the hemoglobin level had fallen to 4.4 Gm. A blood transfusion was started on February 3. After receiving about 100 cc. of blood, the patient com-
plained of chilliness, and the transfusion was discontinued. Shortly afterward his temperature reached 104.4 F. At 6:00 P.M. he felt much better but was extremely prostrated from the chill. At 9:00 P.M. he suddenly became comatose. Convulsive twitchings of the right side of the face and of the left arm and leg were observed at 10:00 P.M. Two hours later, respirations ceased. Permission for autopsy was not obtained.

This patient had received 1,188 Gm. of NaPAB in two courses of therapy. He had glycosuria of 1 to 2 plus while taking the drug.

Case 3. E. N. (Chart 3). This 46 year old Negro woman was admitted to the University Hospital on December 26, 1946, because of intermittent abdominal pain and hematuria of five years' duration. She also gave a history of positive serology for syphilis for one year with inadequate antiluetic therapy. Six

months prior to admission physical examination failed to reveal splenomegaly which was, however, detected three months later when she was re-examined because of excessive ease of fatigue. In this hospital the diagnosis of chronic myelogenous leukemia was made, and a positive Kahn reaction was obtained. The patient was transferred to the Simpson Memorial Institute on January 9, 1947, where examination revealed that the liver and spleen were both enlarged descending to 5 cm. below the right and left costal margins, respectively. On January 15, NaPAB, 24 Gm. daily, was started. At that time the leukocyte count was 155,000 per cu. mm., hemoglobin 8.8 Gm. The red cell packed volume was 59.0 per cent, and the white cell layer was 10.0 per cent. The differential count was as follows: myeloblasts 3.5 per cent, promyelocytes 1.5 per cent, myelocytes 26.5 per cent, metamyelocytes 15.5 per cent, band neutrophils 19.0 per cent, segmented neutrophils 22.0 per cent, eosinophilic myelocytes 0.5 per cent, eosinophils 2.0 per cent, lymphocytes 1.5 per cent, basophils 6.0 per cent, hemophagocytes 2.0 per cent. For six days the NaPAB blood levels ranged from 3.8 to 5.4 mg. per cent and it was, therefore, decided to increase the dosage to 48.0 Gm. daily. Subsequently, her blood levels varied between 10 and 12 mg. per cent. The
fasting blood sugar level was 90 mg. per cent before the beginning of NaPAB therapy, and urine specimens were sugar free. Throughout the period of NaPAB therapy, however, she had glycosuria of 1 to 3 plus. On the twenty-ninth day of treatment her fasting blood sugar level was 73 mg. per cent.

The patient's leukocyte count gradually fell and on February 19 (the thirty-sixth day of treatment), it was 17,600 per cu. mm. The hemoglobin value was unchanged. The spleen decreased in size until the tip was barely palpable at the costal margin. The patient was discharged to her home where she continued to take NaPAB, 16 Gm. daily. A week later the white cells numbered 21,500 per cu. mm. and the hemoglobin had increased to 9.3 Gm. The differential count was very similar to that noted at the beginning of therapy. Ten days later, however, the leukocytes numbered 62,000 per cu. mm., and the amount of NaPAB was increased to 40 Gm. daily. In another week the white cells had risen to 71,750 per cu. mm., but declined to 63,550 per cu. mm. by the following week. Three days later it was necessary to discontinue the medication because of severe nausea. Altogether, the patient had received 1,596 Gm. of NaPAB over seventy days. By April 14, three weeks after her last dose of NaPAB, the white cell count had risen to 199,000 per cu. mm. and the spleen had enlarged to 11 cm. below the left costal margin. The white cell differential count was little changed from the previous ones.

Case 4, C. W. (Chart 4). This patient was a 32 year old white mechanic who was first admitted in February, 1946, when the diagnosis of chronic myelogenous leukemia was made. At that time he received x-ray irradiation therapy over an enlarged spleen, and similar therapy was repeated six months later. He was readmitted to the Simpson Memorial Institute on February 3, 1947, because of progressive ease of fatigue of eight weeks' duration. The spleen descended 12 cm. below the left costal margin, and the liver was palpable 4 cm. below the right costal margin. The hemoglobin was 10.8 Gm. per 100 cc., and the white blood cells numbered 123,000 per cu. mm. Differential count showed myeloblasts 6 per cent, promyelocytes 1 per cent, myelocytes 10 per cent, metamyelocytes 21 per cent, neutrophil band forms 23
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per cent, segmented neutrophils 26.5 per cent, eosinophils 6 per cent, basophils 4 per cent, and lymphocytes 1.5 per cent. The bone marrow was highly cellular with a great increase in granulocyte forms and reduction of erythropoietic elements. Urine analysis was negative. His fasting blood sugar was 47 mg. per cent. Beginning on February 6, the patient received 48 Gm. of NaPAB daily for three weeks when the dosage was decreased to 16 Gm. per day and the patient was discharged. The leukocyte count decreased from 140,000 per cu. mm. on February 6 to 20,500 on February 27, and the hemoglobin fell from 10.8 Gm. to 8.5 Gm. Fasting blood sugar level was 71 mg. per cent on February 25. Glycosuria of 2 to 3 plus was present throughout the period of NaPAB administration. Twelve days later the white count was 22,500 per cu. mm., and the hemoglobin had risen to 10.1 Gm. Despite 26 Gm. daily of NaPAB, the patient’s leukocytes began to increase gradually. On March 21 they numbered 49,750 per cu. mm. and the amount of NaPAB was raised to 40 Gm. daily. A week later the white count was 87,000 per cu. mm., but on the following week it had fallen to 47,000 per cu. mm. The patient continued to take 40 Gm. daily until April 4, when nausea and vomiting forced him to discontinue the medication. When seen again on April 8, the leukocyte count was 46,500 per cu. mm., and the urine was free of glucose. By April 23 the white cells had risen to 115,740 per cu. mm. with a differential count similar to that at the onset of NaPAB therapy. Altogether, this patient received 2,134 Gm. of NaPAB over a period of fifty-eight days.

Case 5. R. M. was a 71 year old white farmer who was well except for mild symptoms of prostatism until September, 1945, when he became aware of a growing mass in the left upper quadrant of the abdomen. Symptoms of anemia developed and he was admitted to the University Hospital in April, 1946, where the spleen was found to be much enlarged, extending below the level of the umbilicus. The hemoglobin value was 11.6 Gm. per 100 cu. mm. and leukocytes numbered 75,000 per cu. mm. The differential count was typical of chronic myelogenous leukemia. The patient received x-ray therapy to the spleen with subsequent improvement in his general condition and decrease in the size of the spleen. In October, 1946, his spleen appeared to be enlarging and he was bothered by a sense of fullness in the abdomen. On March 27, 1947, he was admitted to the Simpson Memorial Institute. At this time the liver descended 5 cm. below the costal margin, and the spleen extended to 6 cm. below the level of the umbilicus.

Repeated urine analyses were negative. The urea clearance test showed 71 per cent of normal in the first hour, and 63 per cent in the second hour. Blood urea nitrogen was 18.0 mg. per cent and the nonprotein nitrogen was 42.6 mg. per cent. The bromsulfalein test for liver function revealed only slight retention of the dye after forty-five minutes. An oral glucose tolerance test was performed after a three day preparatory high carbohydrate diet. The patient received 1.75 Gm. of glucose per kilogram of ideal body weight. The results of this test in milligrams of glucose per 100 cu. mm. of blood were as follows: Fasting, 68; 1 hour after glucose administration, 77; 2 hours, 88; 3 hours, 117; 4 hours, 103; 5 hours, 104; 6 hours, 104; 7 hours, 53. There was 1 plus glycosuria in the second and third hourly specimens, but none at 1 hour, or at the fourth and fifth hours.

NaPAB was administered in dosage of 48 Gm. daily, beginning on March 19, 1947. Before treatment the erythrocytes numbered 4,400,000 and leukocytes 94,500 per cu. mm. The hemoglobin value was 13.0 Gm. per 100 cu. mm. The white blood cell differential count revealed blasts 2.5 per cent, promyelocytes 5.0 per cent, myelocytes 20.0 per cent, metamyelocytes 8.5 per cent, band neutrophils 11.0 per cent, segmented neutrophils 13.0 per cent, eosinophils 10.5 per cent, lymphocytes 1.5 per cent, hemophistiocytes 1.5 per cent, and basophils 6.5 per cent. Glycosuria appeared the day after the NaPAB therapy was started, and persisted throughout the period of treatment.

On April 9, 1947, the oral glucose tolerance test was repeated. Conditions of the test were similar to those before, with the exception that he was now receiving 4 Gm. of NaPAB every two hours, and this was continued throughout the test period as well. The fasting blood sugar level was 56 mg. per cent; 1 hour, 78; 2 hours, 112; 3 hours, 133; 4 hours, 130; 5 hours, 133; 6 hours, 133; 7 hours, 84; 8 hours, 84. There was 2 plus glycosuria before glucose administration, and at the second, third, and fifth hours. A urea clearance test on April 8, 1947, showed 85 per cent of normal in both the first and second hours. The bromsulfalein test was also repeated at this time, and showed no increased retention of the dye.

By April 12, the patient’s leukocyte count had declined to 38,250 per cu. mm., and the hemoglobin level had fallen to 9.1 Gm. The differential count was not significantly altered from that at the beginning of therapy. He was discharged on this date to continue NaPAB therapy at home. While in the hospital the patient received 711 Gm. of NaPAB over sixteen days. He did not return for his scheduled follow-up examination so that additional data are not available.
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Case 6. L. B. The patient was a 66 year old housewife who noted weakness, weight loss, and anorexia beginning in March, 1946. The following month she developed furuncle-like skin lesions over face, neck, and chest. For six years she had had episodes of abdominal distress. She was admitted to the Simpson Memorial Institute on August 17, 1946. There was evidence of chronic illness and pallor. Moderately enlarged firm nodes were present in the neck and axillae. The spleen extended 4 cm. below the left costal margin and the liver was felt 5 cm. below the right lower rib margin. The hemoglobin was 5.6 Gm. per 100 cc., and the white blood cells numbered 20,350 per cu. mm. Differential count revealed many poorly differentiated cells including 46 per cent blast forms. There were 10 nucleated red blood cells per 100 leukocytes. The red cells were bizarre in form and size. Sternal marrow aspiration showed pronounced abnormalities of both erythropoiesis and granulopoiesis. A diagnosis of subacute myelogenous leukemia was made with the subclassification of erythroleukemia. Folic acid, 10 mg. daily, was given for two weeks without any definite effect. On September 4, 1946, the white cell count was 13,000 per cu. mm., and the hemoglobin level was 6.7 Gm. The differential count revealed: myeloblasts 14 per cent promyelocytes 19 per cent, myelocytes 18 per cent, metamyelocytes 17 per cent, neutrophil band forms 20 per cent, segmented forms 8 per cent, hemohistiocytes 2 per cent, and lymphocytes 2 per cent. On September 5, 1946, NaPAB was started in dosage of 24 Gm. daily. Glycosuria was first noted on the day the drug was started and persisted while the medication was continued. Red cell values fell during the period of therapy and two transfusions were given. The drug was discontinued on September 20 after a total of 249 Gm. had been taken. Blood values on that day were as follows: erythrocytes 3,300,000 per cu. mm., leukocytes 13,000 per cu. mm., hemoglobin 5.3 Gm., hematocrit 21.0 per cent; differential count: blasts 14 per cent, promyelocytes 8 per cent, myelocytes 35 per cent, metamyelocytes 16 per cent, band neutrophils 15 per cent, segmented neutrophils 4 per cent, lymphocytes 3 per cent, and hemohistiocytes 1 per cent. By September 25, the white cell count had risen to 45,000 per cu. mm. The patient was discharged and died at home a few weeks later.

Case 7. A. C. This patient was a 43 year old Mexican building laborer who noted ease of fatigue in June, 1946. He was able to continue working until October, 1946, when he began to have episodes of vomiting and abdominal pain. About a month later he developed yellowish pallor, progressive symptoms of anemia, and gingival bleeding. He was admitted to the University Hospital on December 6, 1946. The patient was extremely pale, with a sallow skin color but no icterus of the sclerae. There were a few small nodes in the neck and axillae, the liver was felt 3 cm. below the costal margin, and the spleen could not be palpated. On December 12, the patient was transferred to the Simpson Memorial Institute where a diagnosis of subacute subleukemic myelogenous leukemia was made. Marrow examination of this patient revealed extensive involvement of the erythropoietic as well as the granulopoietic series, and so led to the secondary diagnosis of erythroleukemia as in the preceding case.

Blood values were as follows: Erythrocytes 3,200,000 per cu. mm., leukocytes 8,000 per cu. mm., hemoglobin 6.6 Gm. per 100 cc., hematocrit 32.0 per cent, mean corpuscular volume 96 cu. microns; differential count: myeloblasts 5 per cent, promyelocytes 2 per cent, myelocytes 1 per cent, neutrophils 34 per cent, eosinophils 1 per cent, lymphocytes 35 per cent, hemohistiocytes 1 per cent. There were 20 nucleated erythrocyte elements per each 100 leukocytes counted. Urine analysis was negative. The fasting blood sugar level on December 16 was 71 mg. per cent. On that day, NaPAB was begun in a dosage of 48 Gm. daily. On the following day glycosuria appeared and continued during the period of NaPAB therapy. The fasting blood sugar level was 61 mg. per cent on January 6. The white blood cell count varied considerably, but tended to decrease during the second week of therapy to levels between 2,000 and 3,000 per cu. mm. which were maintained until the NaPAB was discontinued on January 28. On January 14 the patient developed indurated furuncle-like lesions on the thighs. Three of these enlarged and ulcerated. Secondary infection occurred and the lesions remained stationary as large shallow ulcers. Three 500 cc. blood transfusions were given during the NaPAB therapy. Blood values on January 27 were as follows: Erythrocytes 2,000,000, leukocytes 1,800 per cu. mm., hemoglobin 5.0 Gm. per 100 cc., hematocrit 18.0 per cent, mean corpuscular volume 90 cu. microns. The differential count was essentially unchanged from the pretreatment values, except for a relative increase in blast forms.

A series of blood transfusions were given during the following week and the hemoglobin was raised to 12.5 Gm. The white blood cell count increased slightly and was 4,000 per cu. mm. on February 16 when the patient was discharged. Before discharge, a course of x-ray therapy was given to the ulcers on the lower extremities.
The patient returned on February 26. At this time there had been some improvement in the ulcerating lesions on the legs. The hemoglobin had fallen to 10.3 Gm., while the white cell count had risen to 17,300 per cu. mm. There was a striking change in the differential which showed 85 per cent myeloblasts and only 1 per cent mature neutrophils. Late in March the patient was readmitted for a series of plasma transfusions during which the white cells continued to increase in number, reaching 58,500 per cu. mm. with 71 per cent myeloblasts and 15 per cent mature neutrophils.

A glucose tolerance test was performed on April 9. The fasting blood sugar level was 67 mg. per cent. The blood sugar levels of specimens taken at test intervals were as follows: 0.5 hour, 130; 1 hour, 256; 1.5 hours, 184; 2 hours, 240; 2.5 hours, 163; 3 hours, 122; 4 hours, 56; and 5 hours, 50. The fasting urine specimen was negative for glucose as were those obtained at 1, 3, 4, and 5 hours. Only the specimen collected at 2.5 hours gave a reaction (3 plus) for glucose. On April 11, NaPAB therapy was reinstated in a daily dose of 48 Gm. for nine days, when it was discontinued because of nausea and cramping abdominal pain. Glycosuria was again noted during the NaPAB treatment, but disappeared four days after cessation of therapy. The white cell count showed no distinct change during the period of therapy, but during the next nine days it rose from 41,250 to 74,000 per cu. mm.

Case 7, L. D. The patient was a 78 year old white tool grinder who was first seen at the University Hospital in September, 1945, for low back pain of seven years' duration. A diagnosis of spondylitis rhizomelic was made and the patient later received a course of x-ray therapy to the spine at another hospital. In October, 1946, he developed symptoms of anemia which became progressively more severe. He was admitted to University Hospital on December 10, 1946. Examination revealed extreme pallor. Lymph nodes were not enlarged and the spleen was not palpable. On the basis of laboratory findings a diagnosis of subacute myelogenous leukemia was made and the patient was given three transfusions, each of 100 cc. whole blood. On December 28, the patient was transferred to the Simpson Memorial Institute. At that time blood values were as follows: Red blood cells 2,100,000, white blood cells 41,500 per cu. mm., hemoglobin 7.8 Gm. per 100 cc., hematocrit 22.0 per cent; differential count: myeloblasts 22 per cent, promyelocytes 2 per cent, myelocytes 18 per cent, metamyelocytes 13 per cent, band neutrophils 4 per cent, segmented neutrophils 5 per cent, eosinophilic myelocytes 9 per cent, eosinophilic metamyelocytes 9 per cent, lymphocytes 7 per cent, and hemophistiocytes 1 per cent. The fasting blood sugar level was 81 mg. per cent. Administration of NaPAB was begun on December 18, the patient receiving 48 Gm. daily. On the following day glycosuria was noted and this persisted throughout the NaPAB therapy. During the second week of treatment the white cell count began to fall and by January 11, 1947, had reached 8,500 per cu. mm. On January 11, NaPAB was discontinued and on January 14, it was resumed but the dosage was decreased to 14 Gm. daily. Six more blood transfusions were given during the period of therapy with NaPAB. On February 1, 1947, the blood values were as follows: Erythrocytes 3,500,000 per cu. mm., leukocytes 2,200 per cu. mm., hemoglobin 10.1 Gm., hematocrit 33.0 per cent; differential count: myeloblasts 23 per cent, promyelocytes 2 per cent, myelocytes 8 per cent, metamyelocytes 8 per cent, band neutrophils 21 per cent, segmented neutrophils 21 per cent, lymphocytes 11 per cent, and hemophistiocytes 5 per cent. At this time the NaPAB was discontinued and the patient was discharged. He had received 1,130 Gm. of NaPAB over thirty four days. He died at home about two months later.

Case 9, C. K. This patient was a 68 year old white highway construction foreman who had had excellent health until August, 1946, when he developed vague discomfort in the upper abdomen often occurring two or three hours after meals. The following month he lost a considerable amount of weight although his appetite remained normal. In December, symptoms of anemia became prominent and progressed until his admission to the Simpson Memorial Institute on February 3, 1947. Mild symptoms of hypermetabolism had been noted during the three months before admission. Examination revealed extreme pallor, generalized lymphadenopathy, hepatomegaly and splenomegaly. Blood values were as follows: Hemoglobin 4.3 Gm. per 100 cc., red blood cells 1,650,000; white blood cells 255,000 per cu. mm., red cell packed volume 14.0 per cent, white cell packed volume 5.0 per cent; differential count: atypical lymphoid cells 99 per cent, some with notched nuclei, and polymorphonuclear neutrophils 1 per cent. Sternal marrow aspiration revealed almost complete replacement by the abnormal lymphoid forms. Serum bilirubin was 0.65 mg. per cent. On February 6, 1947, NaPAB, 48 Gm. daily, was started. On February 17, the white cell count had fallen to 101,750 per cu. mm. On February 19, a differential count showed no granulocyte forms except for 1 eosinophil in several hundred cells observed. On February 19, the patient had a sudden onset of chills, fever, and cough and NaPAB was discontinued. He had received 634.0 Gm. over fourteen days.
days. In spite of penicillin therapy and supportive measures, the patient died on February 21. On the day before death, the white count had risen to 180,000 per cu. mm. Two plus to 3 plus glycosuria was present during the NaPAB therapy. Autopsy permission was obtained and the pathologic diagnosis was lymphoblastoma of lymphatic leukemia type.

**Case 10.** R. W. This patient was a 77 year old retired white business man who developed an upper respiratory infection late in December, 1946. Early in January he began to notice weakness and malaise and complained of persistence of nasal discharge and a full feeling in his head. A blood count was done and because of the abnormal white count the patient was admitted to the Simpson Memorial institute on February 25. He appeared much younger than his age, but was definitely pale. There were a few small soft lymph nodes palpable in the neck and axillary regions. The spleen was greatly enlarged, extending 7 cm. below the level of the umbilicus. Blood values were as follows: Red blood cells 2,700,000, white blood cells 410,500 per cu.mm., hemoglobin 7.1 gm. per 100 cc., hematocrit 24.0 per cent; differential count: neutrophils 3 per cent, eosinophils 0.5 per cent, monocytes 0.5 per cent, atypical lymphocytes 96 per cent. Sternal marrow aspiration revealed almost complete replacement by the abnormal cells of the type seen in the peripheral blood. The diagnosis was chronic lymphatic leukemia of an atypical type.

NaPAB was started on March 1 in dosage of 48 Gm. daily. On March 4, the dose was reduced to 14 Gm. daily. Glycosuria occurred, usually of two plus degree. On March 11, 1947, auricular fibrillation was noted and digitalis was given. On March 13, the patient received a transfusion of 500 cc. of blood. The NaPAB was discontinued on March 19, 1947, because of nausea, temperature elevation to 101 F., and apparent decrease in the granulocytes of the peripheral blood. The blood values on that day were: Leukocytes 352,500 per cu. mm., hemoglobin 6.6 Gm.; differential count: neutrophils, less than 0.1 per cent, eosinophils 0.5 per cent, and abnormal lymphocytes 99 per cent plus. On March 21 the white blood cells had increased to 538,500 per cu. mm. During the following week the patient was given a course of nitrogen mustard therapy (methyl-bis (beta-chloroethyl) amine). On April 7, the white cell count had fallen to 133,000 per cu. mm., and there were 4.5 per cent neutrophils.

**DISCUSSION**

From the foregoing case reports, it is evident that para-aminobenzoic acid administered in large doses as sodium para-aminobenzoate will bring about a decline in the total leukocyte count of patients with chronic myelogenous leukemia. The fall in white count usually begins during the latter half of the second week of therapy and is most precipitous during the third week. When NaPAB therapy is discontinued, the leukocyte count begins to rise within a few days. Reinstitution of NaPAB administration will again cause a fall in the leukocyte count.

One patient with subacute myelogenous leukemia showed an appreciable fall in the leukocyte count while receiving NaPAB, but little could be evaluated from the results of the administration of NaPAB to the other two patients with subacute myelogenous leukemia of erythroleukemic type.

NaPAB administration was followed by slight decreases in the cell counts of the two patients with lymphatic leukemia, but in these cases therapy was maintained for only fourteen and nineteen days, respectively. It was discontinued primarily because of nausea in one instance, and signs of infection in the other. Both patients then had sharp increases in their leukocyte counts, which were interpreted as evidence that NaPAB had been exerting an effect on the white blood cell level.

Para-aminobenzoic acid in sufficiently high concentration appears to inhibit all phases of granulocyte development in chronic myelogenous leukemia. There was no consistent change in the differential counts of patients receiving this compound and studies of sternal marrow specimens have failed to reveal any "blockage phenome-
non. However, after the first week of treatment, a striking vacuolation of the cytoplasm developed in the myeloblasts and promyelocytes. This change is illustrated in figures 1 and 2 prepared from material obtained by sternal aspiration from patient 3. Figure 1 pictures the marrow prior to the institution of treatment, while figure 2 is of material secured on the thirty-fifth day of NaPAB therapy.

In three of the patients with chronic myelogenous leukemia treated with NaPAB, there was a temporary improvement in the hemoglobin value and the erythrocyte count. There was no apparent effect on the platelets.

![Bone marrow film from patient 3 before treatment showing relative increase in granulocyte forms.](image)

Clinically, the patients were not substantially benefitted by the administration of NaPAB. In some instances the spleen decreased in size, the patients gained weight, and there was a diminution of the symptoms of hypermetabolism. However, these effects were not long maintained after the NaPAB was discontinued. In other patients, there was no objective clinical improvement. Three of the patients died in the hospital, and postmortem examination was performed on one (Case 9). The pathologic findings in this case were largely those of the leukemic process. There were no apparent deleterious effects of the NaPAB.

Although the mechanism of action whereby NaPAB in high concentration disturbs leukocyte proliferation and development is not understood, it appears that the factors which cause and maintain elevated leukocyte counts in leukemia are...
merely inhibited by NaPAB. The possibility that there is an accumulation of these factors during the period of NaPAB administration is suggested by the striking increase in the number of white cells following the cessation of therapy, and by the more gradual leukocyte increases in patients maintained on reduced dosages of NaPAB (charts 3 and 4).

It is also of interest that glycosuria appeared in all of the patients who received NaPAB. A "reducing substance" was noted in the urines of NaPAB treated patients by the U. S. A. Typhus Commission workers but the nature of this substance was not investigated. Our studies have shown that the reduction of Benedict's solution is caused by glucose, as determined by characteristic osazone reactions. Glucose usually appears in the urine within twenty-four hours after the administration of NaPAB is begun and persists for one to four days after it is discontinued. In a few quantitative determinations, the amounts of glucose excreted ranged from 5.0 Gm. to 17.5 Gm. per twenty-four hours.

The basis for glycosuria during NaPAB therapy is being further investigated. Fasting blood sugar levels taken before and during therapy have shown no significant differences. Glucose tolerance studies in two of the patients revealed that the pretreatment renal thresholds for glucose were considerably higher than the
Para-aminobenzoic acid, administered in large doses as sodium para-aminobenzoate caused a striking lowering of the leukocyte counts in five patients with chronic myelogenous leukemia and in one patient with subacute myelogenous leukemia.

NaPAB caused less definite decreases of the white cell count in two patients with chronic lymphatic leukemia, but the periods of administration may have been too short to obtain maximal effects.

In every instance, there was a prompt rise in the number of leukocytes when the administration of NaPAB was stopped.

Although there was decrease in spleen size in some of the patients, the objective clinical improvement was but slight and temporary.

All patients receiving NaPAB in large doses had concomitant glycosuria, apparently on a renal basis.

It is to be emphasized that NaPAB is not considered a practical adjunct to the therapy of leukemia at this time. Rather, it is hoped that studies of the cellular chemistry involved in the apparent inhibitory action of NaPAB may yield information concerning the disordered metabolism of leukemic cells.

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