URETHANE THERAPY IN LEUKEMIA

By ADOLPH J. CRESKOFF, M.D., THOMAS FITZ-HUGH, JR., M.D., AND JOHN W. FROST,* M.D.

The purpose of this paper is to report the results of urethane therapy of the leukemias, based on a study of 24 patients.

In April, 1946, Haddow and Sexton described the influence of various carbamate esters on experimental rat cancers. Ethyl carbamate (urethane) yielded the best results. It alone produced inhibition of tumor growth and fibrous replacement of the cancerous rat tissue. For this reason, and since urethane is relatively nontoxic for humans and is easily obtainable, the experiments were transferred to human subjects with carcinoma of the breast and other malignancies. The results were generally disappointing. It was, however, noted that a few of these patients developed leukopenia while taking urethane. This observation motivated, in 1943, the first clinical trial of the effects of urethane in leukemia and allied disorders.

In May, 1946, Paterson, Haddow, Thomas, and Watkinson reported the results of urethane treatment of 32 leukemic patients. The drug was administered orally in an average dose of 3 to 4 grams daily. The drug proved "effective" in approximately one-third of the patients, producing in this "favorable group" reduction in size of enlarged spleens and of lymph nodes and causing reversion of the blood picture to more normal values. These workers found the urethane effect to be approximately equal in value to that of standard deep x-ray therapy in a control series of similar cases. Of their 32 urethane-treated patients, 19 had myelogenous leukemia; and 8 of these were benefited. Clinical and hematologic remissions were maintained for periods of 2 to 6 months. Of 13 patients with lymphatic leukemia, 2 responded similarly. The remaining 22 were either partially improved, could not tolerate the drug, or died during treatment.

Toxic side effects observed by the British workers included nausea, drowsiness, anorexia, diarrhea, and suggestive evidence of marrow hypoplasia.

On the basis of these results, parallel observations were started at the Hospital of The University of Pennsylvania in June, 1946. At the time of this writing (September, 1947) we have treated a total of 27 patients suffering from leukemia. Three of these are too recently treated for accurate evaluation. Our report is based on the remaining 24.

Dosage and methods of administration. The usual dose of urethane was 4 grams (range 2 to 6 Gm.) daily, given in solution, orally. A mixture similar to that used by the British group was employed in most of the patients.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethane</td>
<td>30 cc</td>
</tr>
<tr>
<td>Syrup of orange</td>
<td>50 cc</td>
</tr>
<tr>
<td>Chloroform water</td>
<td>300 cc</td>
</tr>
<tr>
<td>(each 5 cc contains 0.5 grams urethane)</td>
<td></td>
</tr>
</tbody>
</table>

From the Hematological Section of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia.

This work has been aided by a grant from the Eli Lilly Company.

* Eli Lilly Fellow in Hematology
URETHANE THERAPY IN LEUKEMIA

This mixture was administered (1 to 4 teaspoonsful) after each meal, in a small amount of some flavored carbonated beverage or fruit juice. In a smaller group of patients, the drug was administered in 0.5 Gm. gelatin capsules. This method of administration proved to be impracticable because of the hydroscopic nature of the urethane. Rectal suppositories (each 0.5 Gm. urethane in cocoa butter) were tried in 2 patients who developed nausea from oral medication. Rectal irritation occurred within a few days, requiring cessation of this method of administration.

In one patient (Case 4) with a large leukemic tumor, 50 per cent urethane ointment was employed locally, in conjunction with oral urethane medication. The ointment was prepared by melting urethane crystals and incorporating the solute in aquaphor. The leukemic tumor disappeared under this therapy, although the patient died subsequently.

Urethane intravenously has been our most recent mode of administration. Ampoules* containing 1 or 2 Gm. urethane in 10 cc. of normal saline solution or distilled water, were mixed with 100 cc. of normal saline and the resulting mixture was administered in 15 to 30 minutes intravenously, without untoward reactions.

Clinical material. The results in 14 leukemic patients are reported. Table 1 indicates the distribution of types of leukemia.

<table>
<thead>
<tr>
<th>Type of Leukemia</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Leukemias</td>
<td>10</td>
</tr>
<tr>
<td>Myelogenous</td>
<td>7</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>2</td>
</tr>
<tr>
<td>Monocytic</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Myelogenous Leukemia</td>
<td>7</td>
</tr>
<tr>
<td>Chronic Lymphatic Leukemia</td>
<td>7</td>
</tr>
</tbody>
</table>

RESULTS OF URETHANE THERAPY

Chronic Myelogenous Leukemia.

Our results in 7 cases of chronic myelogenous leukemia are summarized in table 2. It is to be noted that in 4 cases, urethane therapy was started during terminal stages of the disease, after resistance† to x-ray therapy had been established. Two cases are regarded as showing satisfactory clinical and hematologic remissions after urethane therapy. Case 4 is of special interest because of a successful remission maintained despite the complication of pregnancy which is now in its seventh month and is proceeding eventfully.

CASE REPORTS

Case 4. This white female, age 30, first noted weakness, nausea, and abdominal enlargement during the latter months of 1945. When first examined on December 12, 1946, she exhibited massive splenomegaly (19 cm. below the left costal margin), and slight liver enlargement. Blood: Hgb. 8.38 Gm.; WBC 10,000; immature myeloid leukocytes§ 34 per cent. Urethane, 3 Gm. daily, in solution orally, was started on December 14, 1946, and was increased to 4 Gm. daily five days later. By the forty-third day of treatment,* prepared according to our specifications regarding sterility, isotonicity and pH corrections by Dr. F. B. Peck, Eli Lilly Laboratories.

† The term "x-ray resistance" is here employed without implications of any kind except to designate the fact that our own Department of Roentgenology, employing the technics and dosages judged by this Department to be the best under the circumstances, had failed to obtain a remission from one or more recent courses of therapy which formerly in the same patient had produced a remission.

‡ The term "immature myeloid leukocytes" refers to the combined percentage of myelocytes, pro-myelocytes, and myeloblasts.
the spleen measured 11 cm. and the blood count was: Hgb. 9.9 Gm.; WBC 11,000; immature myeloid leukocytes none. The drug was continued until March 22, 1947 (ninety-eighth day), when the spleen measured 5 cm. and the blood showed: Hgb. 13.0 Gm.; WBC 10,000; immature myeloid leukocytes 3 per cent. The patient was symptom-free.

This patient conceived while on urethane therapy. When last seen (Aug. 26, 1947), she was asymptomatic, vigorous, and in the seventh month of pregnancy. The spleen was palpable 6 cm. below the costal rim. Blood: Hgb. 11.4 Gm.; WBC 35,000; immature myeloid leukocytes 7 per cent.

Case 9. White female, age 38. Urethane was first administered during the late stage of chronic myelogenous leukemia of over six years' duration. The patient had failed to respond to her most recent (seventh) course of irradiation. She showed cachexia, lymphadenopathy, and an enormous spleen which al-

<table>
<thead>
<tr>
<th>Case</th>
<th>Original Status</th>
<th>WBC Start U</th>
<th>U (grams)</th>
<th>WBC End U</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Untreated</td>
<td>310,000</td>
<td>256</td>
<td>10,000</td>
<td>Good. Pregnant</td>
</tr>
<tr>
<td>9</td>
<td>Duration 6 years. X-ray resistant</td>
<td>149,000</td>
<td>108</td>
<td>76,000</td>
<td>Died during treatment</td>
</tr>
<tr>
<td>10</td>
<td>Duration 3 years</td>
<td>103,000</td>
<td>13</td>
<td>9,000</td>
<td>Relapsed in 1 weeks. Died</td>
</tr>
<tr>
<td>17</td>
<td>Duration 1 year</td>
<td>43,000</td>
<td>17</td>
<td>20,000</td>
<td>Stopped U because of nausea. Died 2 mo. later</td>
</tr>
<tr>
<td>20</td>
<td>Duration 4 years. X-ray and P32 resistant</td>
<td>395,000</td>
<td>18</td>
<td>120,000</td>
<td>Died during treatment</td>
</tr>
<tr>
<td>22</td>
<td>Duration 2 years. Fowler's solution</td>
<td>55,000</td>
<td>29</td>
<td>14,000</td>
<td>Poor. Given x-ray therapy. Died</td>
</tr>
<tr>
<td>24</td>
<td>Duration 4 years. X-ray therapy in remission</td>
<td>50,000</td>
<td>116</td>
<td>5,100</td>
<td>Good</td>
</tr>
</tbody>
</table>

most filled the abdomen. Blood: Hgb. 7.39. Gm.; WBC 149,000; immature myeloid leukocytes 34 per cent. Urethane, 4 Gm. daily, in solution orally, was started on October 25, 1946, and continued until the patient expired on December 23, 1946. Blood: Hgb. 8.02 Gm.; WBC 76,000; immature myeloid leukocytes 31 per cent.

Case 10. This white male, age 46, was a terminal, much treated case of chronic myelogenous leukemia of over three years' duration. He was readmitted to the hospital in an acute relapse phase of his disease. Urethane, 1 Gm. daily, in solution orally, was given for thirteen days with a fall in the leukocyte count from 103,000 to 9,000. No clinical improvement occurred and the patient died within two weeks after stopping the drug.

Case 17. A white male, age 65, was a terminal case of subacute myelogenous leukemia of one year duration, 'resistant' to irradiation. He was unable to tolerate an adequate dose of urethane either orally or by suppository. A leukemic tumor of his forehead shrank in size and finally disappeared after application of 50 per cent urethane-aquaphor ointment. He died soon thereafter.
Case 20. This white female, age 50, was a leukemic of four years' duration. After numerous courses of irradiation she was finally considered "x-ray resistant." She was cachectic, anasarcatous, and exhibited massive enlargement of lymph nodes, spleen, and liver. Blood: Hgb. 4.95 Gm.; WBC 395,000; immature myeloid leukocytes 52 per cent. Urethane, 2 Gm., then 4 Gm. daily, intravenously was started May 25, 1947, and continued until she died suddenly on June 1, 1947, soon after thoracentesis. On May 31, 1947, she had been clinically unimproved, although her white blood count had dropped to 22,000 on this date.

Case 21. This white male, age 63, had suffered weakness and weight loss for three years. He had just completed a short course of Fowler's solution, when first examined on June 13, 1947. He presented fever, pallor, petechiae, edema, and moderate splenic and lymph node enlargement. Blood: Hgb. 7.5 Gm.; WBC 63,000; immature myeloid leukocytes 33 per cent; Platelets 45,000. Intravenous urethane 2 Gm. was given on June 19, 1947 (WBC 3,000), and was increased to 3 Gm. daily the following day. On June 29, 1947, the drug was stopped after a total of 2.9 Gm. intravenously. The patient was unimproved. Blood: Hgb. 7.5 Gm.; WBC 14,000; immature myeloid leukocytes 13 per cent. Transfusions were ineffective, radioactive phosphorous was given, but the patient died within two weeks.

Case 22. This white female, age 51, was known to have leukemia of four years' duration. She had had several excellent x-ray induced remissions. When seen in the clinic, May 8, 1947, she complained of recent epistaxis and weakness. Her general condition seemed good. The lymph nodes and spleen were not enlarged. Blood: Hgb. 12.4 Gm.; WBC 50,000; immature myeloid leukocytes 17 per cent; Platelets 142,000. Over the next forty-four days, a total of 116 Gm. urethane, in solution orally, was administered. On June 7, 1947, she felt entirely well. Blood: Hgb. 13.2 Gm.; WBC 5,100; immature myeloid leukocytes 2 per cent; Platelets 236,000. When last seen Aug. 12, 1947, she was clinically well. Blood: Hgb. 13.7 Gm.; WBC 16,000; immature myeloid leukocytes 10 per cent.
Chronic Lymphatic Leukemia

Our results in 7 cases of chronic lymphatic leukemia are summarized in table 3. It is of interest that the first case we treated with urethane (Case 1) has now enjoyed an entirely satisfactory remission of slightly over one year's duration.

CASE REPORTS

Case 1. This white female, age 57, first noted weakness, and left-sided "heaviness" in May, 1946. When first examined by us on June 20, 1946, massive splenomegaly and slight lymphadenopathy were found. Blood: Hgb. 11.2 Gm.; WBC 700,000; lymphocytes 96 per cent; Platelets 118,000. Urethane 2 Gm. daily, in solution orally, was started on June 24, 1946, and increased to 4 Gm. daily eleven days later. Marked shrinkage in size of the spleen was apparent after forty-three days of treatment. On September 3, 1946 (seventy-second day of treatment), after a total of 2.83 Gm. of urethane, treatment was stopped. The patient was entirely symptom free; the spleen was barely palpable. Blood: Hgb. 11.4 Gm.; WBC 4,500; lymphocytes 53 per cent.

TABLE 3.—Chronic Lymphatic Leukemia

<table>
<thead>
<tr>
<th>Case</th>
<th>Original Status</th>
<th>WBC Start U</th>
<th>U (grams)</th>
<th>WBC End U</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Untreated</td>
<td>700,000</td>
<td>273</td>
<td>4,500</td>
<td>Good Remission 362 days plus</td>
</tr>
<tr>
<td>#2</td>
<td>Duration 1 year, 1 course x-ray therapy</td>
<td>105,000</td>
<td>191</td>
<td>6,400</td>
<td>Good Remission 184 days plus</td>
</tr>
<tr>
<td>#3</td>
<td>Untreated</td>
<td>58,000</td>
<td>683</td>
<td>11,000</td>
<td>Poor</td>
</tr>
<tr>
<td>#4</td>
<td>Duration 14 years. X-ray 7 months before treatment</td>
<td>233,000</td>
<td>225</td>
<td>8,700</td>
<td>Hem'l: Good. Clin.: Poor. Died at 75 days</td>
</tr>
<tr>
<td>#5</td>
<td>Untreated</td>
<td>238,000</td>
<td>247</td>
<td>293,000</td>
<td>Poor. Given x-ray therapy. Fair response</td>
</tr>
<tr>
<td>#6</td>
<td>Untreated (Leukemia Cutis)</td>
<td>44,000</td>
<td>521</td>
<td>26,000</td>
<td>Poor</td>
</tr>
<tr>
<td>#7</td>
<td>Untreated</td>
<td>265,000</td>
<td>128</td>
<td>32,000</td>
<td>Poor. Hypoplastic marrow</td>
</tr>
</tbody>
</table>

Case 2. This white female, age 54, was found to have "asymptomatic chronic lymphatic leukemia" in September, 1945, and a brief course of irradiation therapy was given. She was first seen in this clinic December 7, 1946. She was still "asymptomatic," there was no lymphadenopathy and the spleen was moderately enlarged. Blood: Hgb. 12.9 Gm.; WBC 102,000; lymphocytes 87 per cent. Urethane 3 Gm. daily, in solution orally, was started. The drug was stopped on February 16, 1947 (seventy-sixth day of treatment), after a total dose of 191 Gm.; her spleen was impalpable; she was still symptom-free, and her blood count was: Hgb. 12.5 Gm.; WBC 6,400; lymphocytes 66 per cent.
The drug was resumed on April 27, 1947, because of a rise in the leukocyte count to 19,800. On May 19, 1947, after a total dose of 69 Gm., urethane was again discontinued when her blood count was: Hgb. 12.0 Gm.; WBC 6,100; lymphocytes 40 per cent. When last seen on August 15, 1947, the patient was still "asymptomatic," her spleen was barely palpable and her blood count was: Hgb. 33.4 Gm.; WBC 11,000; lymphocytes 79 per cent.

Case 6. This white male, age 59, was found in a routine blood count to have 43,000 leukocytes, with 61 per cent lymphocytes. He was asymptomatic, with shotty lymphadenopathy and a barely palpable liver and spleen. Although he required no specific treatment at this time, urethane was started on July 27, 1946, in a dosage of 1 Gm. daily, in solution orally. Blood: Hgb. 14.5 Gm.; WBC 58,000; lymphocytes 89 per cent. No effect of the drug could be detected after 199 days of treatment, (total dose 683 Gm.), and it was stopped on May 15, 1947, when the blood count was: Hgb. 13.0 Gm.; WBC 21,000; lymphocytes 93 per cent.

This case suggests that "low-grade" chronic lymphatic leukemia is resistant to urethane in a dosage of 1 Gm. daily.

Case 7. This white male, age 67, was hospitalized in March, 1944 for prostatic resection. At this time the blood picture of chronic lymphatic leukemia was found. He received a course of irradiation therapy in October, 1945. When first seen in the clinic on November 13, 1946, he was acutely ill, with findings of massive lymphadenopathy, splenomegaly, and marked pulmonary infiltration. Blood: Hgb. 7.5 Gm.;
WBC 233,000; lymphocytes 99 per cent; Platelets 320,000. Urethane, 4 Gm. daily, in solution orally, was started on November 16, 1946. On January 18, 1947 (sixty-second day of treatment), after a total dose of 2.25 Gm., the drug was stopped when the blood count was: Hgb. 6.9 Gm.; WBC 5,600; lymphocytes 93 per cent. The patient had become progressively worse. He died in cardiac failure on January 31, 1947, despite apparent 'improvement' in the abnormal lymphocytosis.

Case 3. This white male, age 61, had sudden severe pain in the left side of the abdomen in November, 1946. Examination disclosed generalized lymphadenopathy, marked splenomegaly, and marked lymphocytosis. Blood: Hgb. 11.4 Gm.; WBC 238,000; lymphocytes 98 per cent. Urethane was started on November 9, 1946, 2 Gm. daily, in solution orally. Dosage was increased to 4 Gm. daily on November 27, 1946, and to 6 Gm. daily on December 5, 1946. Weakness, marked sweating, and insomnia developed. On January 6, 1947, lymph nodes were estimated 80 per cent reduced in size but the size of the spleen was unchanged. Blood: Hgb. 11.1 Gm.; WBC 400,000. The dosage of urethane was decreased to 4 Gm. daily until January 10, 1947 (sixty-third day of treatment) when it was discontinued (total dose 2.97 Gm.). Blood: Hgb. 12.2 Gm.; WBC 239,000; lymphocytes 97 per cent. X-ray therapy was instituted with prompt fall in the leukocyte count, but little change in size of lymph nodes or spleen. When last examined on August 25, 1947, moderate splenomegaly and lymph node enlargement were found. His blood count showed: Hgb. 33.6 Gm.; WBC 38,000; lymphocytes 93 per cent.

This case is judged a urethane failure. Although regression in lymph node size occurred there was no improvement in the splenomegaly or in the blood picture.

Case 13. This white male, age 52, presented generalized exfoliative dermatitis, lymphadenopathy, and lymphocytosis, diagnosed as leukemia cutis, of six months' duration. Urethane, 4 Gm. daily, in solution
orally, was started on January 7, 1947. Blood: Hgb. 13.0 Gm.; WBC 44,000; lymphocytes 83 per cent. No change in the patient's clinical condition was apparent when the drug was stopped 136 days later (total dose 52.1 Gm.). Blood: Hgb. 5.5 Gm.; WBC 2.1,000; lymphocytes 33 per cent.

**Table 4.—Acute Leukemia**

<table>
<thead>
<tr>
<th>Case</th>
<th>Original Status</th>
<th>WBC Start U</th>
<th>U (grams)</th>
<th>WBC End U</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>#2</td>
<td>W 50 F Untreated Monocytic</td>
<td>35,000</td>
<td>60</td>
<td>1,100</td>
<td>Good initial, but relapse 3 mo.</td>
</tr>
<tr>
<td>#5</td>
<td>W 53 F Untreated Myelogenous</td>
<td>79,000</td>
<td>16</td>
<td>8,000</td>
<td>Poor. Died</td>
</tr>
<tr>
<td>#11</td>
<td>W 14 F Untreated Myelogenous</td>
<td>240,000</td>
<td>64</td>
<td>250,000</td>
<td>Poor. Died</td>
</tr>
<tr>
<td>#12</td>
<td>W 12 F Untreated Lymphatic</td>
<td>1,800</td>
<td>14</td>
<td>900</td>
<td>Poor. Died. Aplastic marrow</td>
</tr>
<tr>
<td>#14</td>
<td>W 42 M. Untreated Myelogenous</td>
<td>77,000</td>
<td>48</td>
<td>49,000</td>
<td>Poor. Died</td>
</tr>
<tr>
<td>#15</td>
<td>W 15 M Untreated Myelogenous</td>
<td>221,000</td>
<td>137</td>
<td>149,000</td>
<td>Poor. Died 1 mo. after treatment</td>
</tr>
<tr>
<td>#18</td>
<td>C 3 F Untreated Myelogenous</td>
<td>56,000</td>
<td>16</td>
<td>300</td>
<td>Fair for 1 mo. then relapse. Marked decrease in size of kidney masses</td>
</tr>
<tr>
<td>#19</td>
<td>C 38 M Untreated Myelogenous</td>
<td>110,000</td>
<td>67</td>
<td>9,500</td>
<td>Left hospital. No follow-up</td>
</tr>
<tr>
<td>#21</td>
<td>W 36 M Untreated Lymphatic</td>
<td>100,000</td>
<td>14</td>
<td>39,000</td>
<td>Poor. Died</td>
</tr>
<tr>
<td>#23</td>
<td>W 5 F Untreated Myeloblastic</td>
<td>131,000</td>
<td>3</td>
<td>2,700</td>
<td>Poor. Died</td>
</tr>
</tbody>
</table>

*Case 16.* This white male, age 45, noted enlargement in circumference of neck in December, 1946. When first seen on January 28, 1947, he presented generalized lymphadenopathy and moderate splenomegaly. Blood: Hgb. 13.9 Gm.; WBC 265,000; lymphocytes 93 per cent; Platelets 111,000. Urethane, 3 Gm. daily, orally, first in solution, then in capsules was started on January 27, 1947. The dose was soon increased to 4 Gm. daily. By March 20, 1947 (fifty-first day of treatment), dangerous symptoms of drowsiness, weakness, anorexia, fever, petechiae, mucosal bleeding, and hematuria appeared. Blood: Hgb. 7.52 Gm.; WBC 51,000; lymphocytes 93 per cent; Platelets 50,000. On April 1, 1947 (sixty-third day of treatment), after a total of 2.18 Gm., the drug was stopped. No significant changes in lymph node or splenic size were
demonstrable. Multiple transfusions, followed by cautious x-ray irradiation produced slow improvement with cessation of hemorrhagic phenomena and marked reduction in the size of lymph nodes. The blood picture improved, and when last seen on August 25, 1947, his blood count showed: Hgb. 13.20 Gm.; WBC 81,000; lymphocytes 79 per cent; Platelets 64,000.

This case is obviously another urethane failure. It is possible that the drug produced critical hypoplasia of erythrocytic and megakaryocytic elements in the bone marrow.

**Acute Leukemias**

Table 4 summarizes the results in 10 cases of acute leukemia of various types. In most cases, a prompt fall in the total leukocyte count followed urethane treatment. Evanescent clinical improvement occurred in 4 patients (Cases 2, 15, 18, 19). Final information regarding 2 patients in this series is not available. All other patients died during or soon after urethane therapy.

**CASE REPORTS**

**Case 2.** This white female, age 40, had acute monocytic leukemia (Naegeli type) with fever, gingival necrosis, and extensive intracutaneous and mucosal bleeding of 2 weeks duration. Urethane, 4 Gm. daily, in solution orally, was started on August 11, 1946. Blood: Hgb. 7.2 Gm.; WBC 35,000; immatures (promonocytes and monoblasts) 64 per cent. A total of 60 Gm. was given during the next ten days with rapid fall in leukocytes to 1,100, then to 650/cu. mm. Progressive anemia paralleled the fall in leukocytes. On September 4, 1946, the blood count showed: Hgb. 1.38 Gm.; WBC 1,300; immatures 16 per cent. Despite these desperately low blood levels the patient felt improved, the gums healed and bleeding ceased. There was gradual improvement and when the patient was sent home on October 45, 1946, the blood count was: Hgb.4.95 Gm.; WBC 1,400; immatures 36 per cent.

It is noteworthy that sternal aspiration soon after termination of therapy showed striking reduction in numbers of blast cells as compared with the original aspiration.

**Case 5.** White female, age 53. Acute myelogenous leukemia. Urethane, 2 to 4 Gm. daily, in solution orally, was started on June 30, 1946 when the blood showed: Hgb. 12.4 Gm.; WBC 79,000; immatures (promyelocytes and myeloblasts) 82 per cent. Four days later the patient exhibited a phlebothrombosis of the right leg. On July 9, 1946, urethane was discontinued (total dose 16 Gm.). Blood: Hgb. 9.2 Gm.; WBC 8,000. On July 13, 1946, the leukocyte count rose to 31,000 and urethane, 4 Gm. daily, orally was resumed. The patient died suddenly of pulmonary embolism, July 31, 1946, after a second course of 10 Gm. of urethane when the blood count was: Hgb. 7.9 Gm.; WBC 16,000.

**Case 11.** White female, age 14. This patient had acute myelogenous leukemia of two weeks' duration, with generalized lymphadenopathy, hepato-splenomegaly, gingivitis, mucosal and intracutaneous bleeding. On December 44, 1946, the blood count showed: Hgb. 12.2 Gm.; WBC 360,000; blast cells 89 per cent. A total dose of 68 Gm. of urethane was given between December 30, 1946 and January 7, 1947, when the patient died after a progressively downhill course: Blood: Hgb. 6.2 Gm.; WBC 250,000.

**Case 12.** White female, age 11. This patient had acute aleukemic lymphatic leukemia with hemolytic staphylococcus aureus sepsisemia. Urethane, 4 Gm. daily, in solution orally was started on April 7, 1947.
Blood: Hgb. 6.17 Gm.; WBC 1,800; blast cells 82 per cent. Urethane was discontinued April 14, 1947 (total dose 14 Gm.), when the blood count showed: Hgb. 6.6 Gm.; WBC 900. Death occurred April 22, 1947, despite multiple transfusions and penicillin therapy.

Sections of marrow obtained at autopsy showed almost complete aplasia in contrast to the initial sternal marrow appearance of acute lymphoblastic leukemia.

**Case 14.** White male, age 42. This patient had acute myelogenous leukemia and was moribund on admission. He was given 6 Gm. urethane daily, in solution orally, for eight days without detectable effect clinically or hematologically. The patient died August 2, 1947 while still under therapy.

**Case 15.** White male, age 15. Acute myelogenous leukemia. He had received 115 Gm. urethane orally in 32 days, while in another hospital, with a fall in leukocytes from 211,000 to 19,300, but without clinical improvement.

Urethane, 3 to 4 Gm. daily, orally in solution, was reinstated March 1, 1947. Blood: Hgb. 13.8 Gm.; WBC 74,000; immatures (blasts) 96 per cent. Because of severe nausea, vomiting, and diarrhea the drug was stopped March 8, 1947 (total dose 141 Gm.). WBC 125,000. Irradiation therapy was started March 10, 1947 and given daily until discharged at his request on March 19, 1947, when his blood count showed: Hgb. 7.4 Gm.; WBC 173,000. This patient died two weeks later.
Case 18.* Colored female, age 3. Acute myelogenous leukemia. This patient had been ill for one month. The outstanding physical finding was the presence of huge bilateral renal masses. Urethane, 2 Gm., daily in solution orally, was started March 11, 1947, when the blood count was: Hgb. 4.3 Gm.; WBC 41,000; immatures (blast cells) 40 per cent. By March 19, 1947, the renal masses had decreased markedly in size (by palpation and urography). The drug was stopped on March 24, 1947, when the blood count showed: Hgb. 4.6 Gm.; WBC 1,100; immatures none. The patient seemed temporarily improved, but relapsed and died one month later.

Case 19. Colored male, age 38. Acute myelogenous leukemia. Urethane, 3 Gm. intravenously was started on May 9, 1947, and increased to 4 Gm. daily the following day. Blood: Hgb. 2.1 Gm.; WBC 110,000; immatures (promyelocytes and myeloblasts) 90 per cent. On May 25, 1947, after a total of 67 Gm. intravenously, the patient showed improvement in strength and a 50 per cent decrease in the size of the lymph nodes. The blood count at this time showed: Hgb. 5.9 Gm.; WBC 9,500; immatures 73 per cent. After receiving 2,000 cc. of whole blood the patient was discharged June 10, 1947 when the blood count showed: Hgb. 7.8 Gm.; WBC 5,500; immatures 69 per cent. It has been impossible to obtain further information regarding this patient.

* This case observed at Philadelphia General Hospital, courtesy of Dr. Paul Gyorgi.
**URETHANE THERAPY IN LEUKEMIA**

**Case 21.** White male, age 30. Acute lymphatic leukemia. This patient had been given 28 Gm. of urethane in fourteen days, elsewhere, with fall in leukocyte count from 200,000 to 39,000. He was admitted to the Hospital of The University of Pennsylvania on May 26, 1947, in poor condition, and given preliminary dose of 3 Gm. urethane, intravenously at which time the blood count was: Hgb. 8.8 Gm.; WBC 21,000; immatures (prolymphocytes and lymphoblasts) 35 per cent. The dose was changed to 4 Gm. daily on May 27, 1947, and again to 6 Gm. daily on June 13, 1947. Blood: Hgb. 6.9 Gm.; WBC 109,000; immatures 99 per cent. A total of 106 Gm. urethane, intravenously, had been given over a twenty-four day period when this patient died June 20, 1947. The blood count then was: Hgb. 8.6 Gm.; WBC 132,000. The patient had also received 5,000 cc. of whole blood during his hospital stay.

**Case 23.** White female, age 5. Acute myelogenous leukemia. One Gm. urethane, intravenously, was given June 8, 1947, when the blood count was: Hgb. 7.02 Gm.; WBC 132,000; blasts 90 per cent. On June 9, 1947, 2 Gm. urethane was given intravenously. This was followed by a sudden rise in temperature to 105.2 F., rectally. Urethane therapy was discontinued. On June 11, 1947, marked diminution in splenic size was noted, and the blood count was: Hgb. 6.13 Gm.; WBC 2,700. The patient died June 17, 1947, with a Hgb. of 4.73 Gm.; and a WBC of 750/cu. mm.
Summary of Results

It is apparent from the data presented above that satisfactory remissions as a result of urethane therapy occurred in 4 cases (1, 3, 4, 24) of our combined number of 24 cases. It is worthy of emphasis that of these 24 cases, at least 14 (Cases 9, 10, 17, 20; and all acute leukemias) and possibly 2 others (Cases 7 and 21) would, in our opinion, have proved hopelessly refractory to any known method of treatment of leukemia. It may be significant also that although urethane was withdrawn in Cases 8 and 13 because of poor response, these patients subsequently responded poorly to irradiation and radioactive phosphorous, respectively.

If the experimentally treated 4 terminal cases of chronic myelogenous leukemia are omitted from consideration, it is apparent that urethane produced a satisfactory result in 2 of the 3 remaining cases. Adequate response was obtained in 2 of 7 cases of chronic lymphatic leukemia. It becomes evident that of 10 “fair” cases of chronic leukemia, urethane was successfully used in 4.

Drug Effects

Toxicity. Nausea has been the predominant symptom of intolerance. Approximately 50 per cent of our patients exhibited mild or severe nausea commencing at any time during the course of oral administration of the drug. In a few cases, nausea was sufficiently severe to warrant interruption or cessation of treatment. Lesser toxic manifestations have been vomiting, anorexia, excessive sweating, diarrhea, and drowsiness.

The most dangerous toxic manifestation has been the appearance of evidence suggesting depression of all marrow elements (Cases 12, 16). Whether or not urethane produced or contributed to this effect, it is important to be wary of abrupt falls in erythrocyte or leukocyte levels during the period of urethane administration. It is significant that 2 patients in Paterson’s series exhibited similar hypoplastic changes. Particular caution is advisable when leukopenic leukemia is under treatment, on the basis of Case 12. Rapidly developing anemia, in our experience, calls for immediate cessation of urethane therapy.

Urethane administered intravenously has produced only minimal side effects, such as transitory drowsiness, and transitory elevation of temperature. No local irritative phenomena have been observed. Particularly gratifying has been the absence of nausea, suggesting that the occurrence of this symptom after oral administration is due to gastric irritation. It is possible that enteric coated capsules or tablets may circumvent such nausea, and trials with such preparations are in progress.

Rapidity of effect. The time required for a definite reduction in the leukocyte count (to 15-20,000) in favorable chronic cases averaged forty-eight days when the drug was given by mouth. In the acute leukemias, the effect was much more rapid, averaging ten days. It is believed that intravenous administration of urethane will produce effects more quickly than the above mentioned periods, although our data are as yet insufficient to establish this point.

Mode of action. The manner and site of action of urethane are entirely unknown.
Haddow and Sexton offer speculation regarding the possible action of urethane in remedying some deficiency in the process of leukocytic maturation in leukemia.

**Basal metabolism and blood chemistry.** In a small number of patients with chronic forms of leukemia, we observed that the basal metabolic rate fell in proportion to the decline in the total white cell count during urethane therapy.

Marked reduction in elevated levels of blood uric acid was also noted in a few of our cases during therapy. Case 19 had a blood uric acid of 11.3 mg. per 100 ml. on admission, which fell to 3.8 mg. per 100 ml. at the end of urethane therapy when the white blood count was 8,000. Case 4 had a reduction of blood uric acid from 8.9 mg. per 100 ml. to 4.2 mg. per 100 ml. while under urethane therapy.

Blood urea nitrogen determinations were made before, during, and after urethane administration in 10 of our cases. Elevation of the level of blood urea nitrogen occurred in no case during full urethane dosage.

Blood levels of urethane have not been obtained. A method of estimation has recently been published by Archer et al.

**Discussion**

Urethane adequately administered in cases of chronic leukemia frequently produces a marked reduction in the total leukocyte count (83.3 per cent of our series). In fully responsive, favorable cases definite clinical improvement gradually follows. Splenomegaly is reduced, enlarged lymph nodes become smaller, and a feeling of betterment is expressed. The hemogram assumes a more normal appearance in its entirety. Unfortunately, in a larger number of cases the fall in the leukocyte count is a spurious improvement. In such cases, visceral pathology and anemia may fail to improve or may grow worse, and the patient may exhibit progressive deterioration. Continued administration of the drug in such instances may lead to rapid clinical deterioration. It is generally advisable to suspend the drug if clinical improvement fails to appear within one week after a satisfactory rate of fall of the leukocyte count has appeared. It is furthermore probably advisable to discontinue urethane if no significant fall in the white cell count has occurred within sixty days from the start of treatment.

It is impossible, from our small series of cases, to offer definite criteria for selection of patients for urethane treatment. It seems likely (in agreement with Paterson et al.) that chronic myelogenous leukemia responds better to urethane than does the lymphatic variety. The drug has proved of little value in the acute leukemias, although further trials are justifiable in view of the swiftly fatal outcome of this form of leukemia.

No information is as yet available as to the possibility of inducing repeated remissions in chronic leukemia with urethane, and if so, whether these can then be followed by successful repetitions of x-ray therapy. If this should prove the case, then prolongation of the leukemic life-span as well as amelioration of symptoms may be possible. In this regard it may be mentioned that in Cases 3 and 24, urethane successfully induced remissions after relapse from previously successful x-ray therapy. Conversely, in 2 other cases (8 and 16), x-ray therapy successfully followed urethane failures. This is in accord with the observation of the British
workers that urethane and irradiation therapy are not mutually exclusive in effect. Our evidence does indicate strongly that urethane is without clinical effect in terminal, long standing, repeatedly irradiated cases of chronic leukemia.

It is our impression that urethane will prove to be an occasionally useful adjunct in the management of chronic leukemia. The low cost and convenience of administration, in comparison with irradiation therapy are strong points in favor of this drug.

It is the opinion of the authors that in the treatment of leukemia in general, urethane is less consistent in effect than standard methods of irradiation therapy, and more consistent and more efficient than such modalities as Fowler's solution, benzol, and colchicine.

Our results, while not as striking, generally confirm the findings reported by Paterson and her co-workers. Urethane deserves further trial in the treatment of leukemias of all types.

**Summary**

1. The results of urethane therapy in 24 cases of leukemia are described.
2. The average daily dose is 4 Gm. orally or intravenously.
3. The drug is irregularly effective. Chronic myelogenous leukemia appears more responsive than the lymphatic variety.
4. Acute leukemias are not significantly altered in course by urethane.
5. Urethane produces a fall in the total leukocyte count in a majority of all types of leukemia. Clinical improvement does not necessarily follow.
6. Nausea is the most frequent side effect of urethane therapy. Possible marrow aplasia is the most dangerous toxic effect.
7. Urethane is of definite, but of limited value in the treatment of chronic leukemia. In some instances, it compares favorably with x-ray therapy, but in general, it is less dependable, particularly in its frequent failure to induce optimum return of normal red cell and platelet values, and optimum regression of organ infiltration.

**References**

URETHANE THERAPY IN LEUKEMIA

ADOLPH J. CRESKOFF, THOMAS FITZ-HUGH, JR. and JOHN W. FROST