URETHANE (ETHYL CARBAMATE) THERAPY IN MULTIPLE MYELOMA

By J. Philip Loge, M.D., and R. Wayne Rundles, M.D.

INTEREST in the growth-suppressive properties of the carbamic esters, known for many years from general biologic studies, was renewed in 1945 by the investigations of Templeman and Sexton. In studying the effect of ethyl phenylcarbamate on the growth of plant seedlings, they confirmed the earlier work of LeFèvre showing that this chemical retarded or even arrested plant growth, with various structures undergoing bulbous hypertrophy. Cytologically it appeared that mitosis was blocked in pseudometaphase, leading to the irregular formation of monstrous nuclei. Haddow and Sexton then studied the effect of different carbamic esters on experimental animal tumors. They found that the common urethane, ethyl carbamate, was the most promising compound. It produced a transient increase in mitosis in normal tissues, and a significant retardation in the growth of spontaneous mammary cancer in the mouse and in the growth of the Walker rat carcinoma 256. The histologic structure of the tumors was profoundly altered.

Clinical trials using urethane and isopropyl phenylcarbamate in the treatment of advanced inoperable cancer were then undertaken. Amelioration was observed in a few cases but the results were generally disappointing. It was noted, however, that a fall in the leukocyte count occurred with some regularity. The experiments were then modified to include myeloid and lymphatic leukemia. Here the effects were vastly more pronounced, indeed comparable in many ways to those obtained by roentgen irradiation. Following the report of Paterson, AplThomas, Haddow, and Watkinson, urethane began to be used extensively in the treatment of leukemias and widespread tumors in clinics throughout the world.

The therapeutic limitations of urethane have become clearer as experience has widened. In disseminated cancer, in spite of an occasional success, there is usually no benefit from this therapy. In localized lymphomas, roentgen irradiation remains the treatment of choice. In acute leukemias, there is generally no improvement. In chronic leukemias the net clinical benefit in many cases is probably less than that obtainable by standard methods of treatment. A disease in which exceptional therapeutic results may occur, however, is multiple myeloma, for changes have been observed following urethane administration which appear to be unique in the therapy of this disease.

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The major features of multiple myeloma have been reviewed recently by Bayrd and Heck and Lichtenstein and Jaffe. It is a uniformly malignant disease progressing to a fatal termination in an interval varying from a few weeks to sometimes several years. The disease results essentially from the excessive proliferation of abnormal plasma or 'myeloma' cells within the bone marrow. Anemia, leukopenia and at times thrombocytopenia result. Skeletal support becomes seriously impaired as the bones soften due to diffuse demineralization or to the formation of multiple areas of osseous destruction showing virtually no detectable attempt at repair. A complex abnormality of the body proteins is a feature of the disease being manifested by abnormally high serum protein values, hyperglobulinemia and often Bence-Jones proteinuria. Grave renal disease is a commonly associated finding.

Many different types of therapy have failed to alter significantly the clinical course of multiple myeloma. Roentgen irradiation, which has been used extensively, is fairly effective in relieving localized bone pain. Radioactive phosphorous, likewise, may relieve skeletal pain but even with doses large enough to produce leukopenia and thrombocytopenia there has been no overall improvement. A few patients with multiple myeloma have been treated with nitrogen mustard compounds but the results have been disappointing. Myeloma cells do not decrease in number in the bone marrow and there is no change in the histologic structure as observed in serial biopsies.

Another approach to the chemotherapy of multiple myeloma was introduced by Snapper who used injections of stilbamidine and pentamidine combined with a diet low in animal protein. Symptomatic improvement and even bony recalcification was noticed in some patients. Myeloma cells persisted in the bone marrow without quantitative decrease, however, as did Bence-Jones proteinuria and hyperglobulinemia. Relapses occurred. Serious toxic reactions limited the usefulness of the diamidine compounds. Antimony compounds were used by Rubinstein with similar results.

Reports of urethane therapy in patients with multiple myeloma are few. Patterson and her co-workers observed no improvement after giving urethane to 2 patients with multiple myelomatosis. Berman and Axelrod gave 72 Gm. of urethane to a 51 year old man with multiple myeloma but discontinued therapy when leukopenia developed. Hyperglobulinemia and Bence-Jones proteinuria was unchanged. Serial x-rays showed no change. Alwall used urethane in the treatment of two patients with multiple myeloma. To one who complained mainly of skeletal pain he gave 3-4 grams of urethane daily for three months, without noticable improvement. Stilbamidine was then injected intravenously and he was rather promptly relieved of pain. Other aspects of the disease were not affected. A second patient whose complaints related to anemia was given urethane alone and observed over a period of eight months. The anemia, albuminuria, hyperglobulinemia, and rapid sedimentation rate all improved considerably during the first four months of treatment and myeloma cells could no longer be found in the bone marrow.

This spectacular but isolated result suggested to us a more extensive and pro-
longed trial of urethane therapy in multiple myeloma. We have now studied the early therapeutic responses of 4 patients to urethane during observation and follow-up periods ranging from seven to thirteen months. Other types of specific therapy have been withheld. The detailed case histories follow.

**Table 1.—Case 1, C. F. H., B-25130, Hematologic Findings**

<table>
<thead>
<tr>
<th>Date 1948</th>
<th>Hgb. Gm per 100 cc.</th>
<th>RBC mill. per c.mm.</th>
<th>WBC 1000</th>
<th>Hematocrit %</th>
<th>Reticulocytes</th>
<th>Platelets thousands per c.mm.</th>
<th>Differential WBC and therapy</th>
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</thead>
<tbody>
<tr>
<td>1/30</td>
<td>8.1</td>
<td>2.7</td>
<td>9750</td>
<td>25</td>
<td>1.6</td>
<td>1000</td>
<td>Neutrophils 42, stab 8, metamyelocytes 6, myelocytes 3, myeloblasts 1, lymphocytes 30, monocytes 7, plasma cells 3, normoblasts 3/100 WBC.</td>
</tr>
<tr>
<td>1/18</td>
<td>7.1</td>
<td>2.4</td>
<td>10950</td>
<td>21</td>
<td>2.7</td>
<td>480</td>
<td>Urethane 6 Gm./day</td>
</tr>
<tr>
<td>2/21</td>
<td>6.6</td>
<td>2.3</td>
<td>19000</td>
<td>20</td>
<td>1.6</td>
<td>316</td>
<td>Urethane 1.5-2.0 Gm./day</td>
</tr>
<tr>
<td>3/2</td>
<td>7.0</td>
<td>2.4</td>
<td>6150</td>
<td>21</td>
<td>1.5</td>
<td>530</td>
<td>(220 Gm.)</td>
</tr>
<tr>
<td>3/9</td>
<td>6.6</td>
<td>2.5</td>
<td>2900</td>
<td>22</td>
<td>4.2</td>
<td>560</td>
<td>Bone Marrow: Plasma cells 98, neutrophils 1, monocytes 0.5, lymphocytes 0.5.</td>
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<tr>
<td>3/16</td>
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<td>2.8</td>
<td>1600</td>
<td>14</td>
<td>8.7</td>
<td>112</td>
<td>Neutrophils 71, stab 3, lymphocytes 20, monocytes 6.</td>
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<tr>
<td>4/9</td>
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<td>3500</td>
<td>29</td>
<td>6.0</td>
<td>1330</td>
<td>Bone Marrow: Plasma cells 1, neutrophils 9, stab 16, metamyelocytes 9, myelocytes 10, myeloblasts 3, lymphocytes 2, monocytes 1, macrophages 1, reticulum cells 1, eosinophils 2, erythroblasts 3, basophilic normoblasts 15, acidophilic normoblasts 23.</td>
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<td>4/19</td>
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<td>4900</td>
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</table>

**Case Reports**

**Case 1, C. F. H., Unit No. B-25130.** This 41 year old colored woman was referred to Duke Hospital on January 28, 1948. Her health had been good until six months earlier when she began to have chest pain when coughing or when pressure was exerted against her ribs. In the course of another two or three months she was forced to quit work because of pain along the spine and about her hips. The skeletal pain increased progressively. During her last month at home she was unable to walk or even get out of bed. She lost about ten pounds in weight.

Physical examination showed her to be a well developed, well nourished colored woman unable to move about on the examining table without acute discomfort. Pressure over the sternum, ribs, and spines of the vertebrae was exquisitely painful. The remainder of the examination disclosed no relevant abnormalities.

Examination of the peripheral blood showed that there was a severe anemia with immature granulocytes, plasma cells and nucleated red cells in the circulating blood (table 1). Rouleaux formation was
conspicuous in the blood films. Urinalysis showed a small amount of protein and a trace of Bence-Jones protein. The excretion of phenolsulphophthalein dye was not impaired. Serologic tests for syphilis were negative. The serum proteins were 13.2 Gm. per 100 cc. with 4 Gm. of albumin and 9.2 Gm. of globulin on one determination, and 10 Gm. with 3.4 Gm. albumin and 6.6 Gm. globulin on another (table 5). The blood calcium was 12.4 Gm. per 100 cc., phosphorus 3.6 Gm., and alkaline phosphatase 3.1 Bodansky units per 100 cc. A bromsulfalein test of liver function, using 5 mg. of dye per kilogram of body weight, showed 7 per cent retention after 45 minutes. Roentgen examination of the skeleton (fig. 1 A and B) showed pronounced generalized demineralization with small and large areas of non-reactive destruction in the skull, ribs, vertebrae, pelvis and long bones. There was partial collapse of the ninth and twelfth thoracic vertebrae.

Bone marrow was obtained by sternal aspiration. The bone was so soft that there was almost no resistance to insertion of the needle. In the stained films the marrow was exceedingly cellular. In most areas there were virtually no cells other than abnormal plasma cells (fig. 1, C). These varied from the size of the ordinary plasma cells to some two or three times as large. Many had double or triple nuclei. The latter contained one, two, or even three prominent nucleoli, some as large as one-half the diameter of the nucleus.

The patient was admitted to the hospital on 1/18/48 for a trial of urethane therapy. The drug was tolerated well in divided doses by mouth and, between 2/11/48 and 3/9/48, 85 Gm. were given. A leukocytosis of 19,000 developed on the fourth day of therapy. The white blood count then gradually fell to 2,900 on the sixteenth day. Urethane was withheld for seventeen days after which it was resumed in a dose of 1.5 to 2 Gm. per day until another 35 Gm. had been administered. During the first two weeks in the hospital her temperature ranged from 37 C. to 38.3 C. with one rise to 39.6 C. Afterwards her temperature was normal. Bone pain gradually became less until she was entirely comfortable while resting in bed. After one month in the hospital she was able to return home. There she gradually extended her activity until she could sit at the table with her family for meals and walk by holding to furniture. Pain of sciatic radiation developed after a period of over exertion but this subsided when her activity was again restricted. Three and one-half months after the beginning of therapy she was able to walk unaided and without difficulty.

The peripheral blood values (table 1) showed progressive improvement following the administration of urethane. Immature granulocytes, plasma cells and nucleated red cells disappeared in a few weeks from the circulating blood. After two months of therapy, the bone marrow was re-examined. An exceedingly cellular marrow was again obtained but the predominant cells were now normal erythroid and myeloid elements (table 1). Scattered through the films there was an occasional small cluster of plasma cells greatly altered in morphology (fig. 1, E). Their cytoplasm was now irregular in contour, stained a denser blue and often contained light areas suggestive of early vacuolization. Their nuclei were extremely eccentric and pyknotic. Basophilic granules in the cytoplasm such as occur following stilbamidine and antimony therapy were not present. A few of the plasma cells had developed into giant forms nearly as large as megakaryocytes (fig. 1, D). The total number of plasma cells comprised but 1.0 per cent of the total marrow cells. Megakaryocytes, many showing platelet formation, were present in about normal numbers. Other marrow elements were not detectably abnormal.

On a check-up examination three and one-half months after the beginning of treatment the plasma proteins had fallen to 8.1 Gm. per 100 cc., with 5.0 Gm. albumin and 3.1 Gm. of globulin (table 5). The bromsulfalein test repeated as before showed but a trace of the dye remaining in the serum at 45 minutes. The alkaline phosphatase was 6.7 Bodansky units, calcium 10.6 mg. per 100 cc., and phosphorus 2.9 mg. Bence-Jones proteinuria and albuminuria were not present.

Improvement in her general health continued during the following five months. The peripheral blood values became normal (table 1). Repeated bone marrow examinations failed to show abnormal numbers or types of plasma cells. The blood chemical values remained unchanged. Skeletal x-rays showed gradual recalcification of the vertebrae, pelvis and upper femora. She began to complain of lower abdominal pain radiating into her right thigh, and examinations showed progressive anterior displacement of a fibroid uterus. A laparotomy was performed and the iliac vessels and mesocolon were infiltrated with a fleshy retroperitoneal tumor. Resection was attempted. She died two days later of uncontrolled hemorrhage nine months after the beginning of urethane therapy. Pathologic examination of the resected tissue showed it to be a myeloma tumor.
FIG. 1. Case 1, C. F. H., Unit No. B-25150

A. & B. Roentgenograms showing extensive bony destruction in ribs, vertebrae, pelvis, upper ends of femurs, and skull before treatment.

C. Photograph of aspirated sternal marrow before treatment (X 600) showing preponderance of abnormal plasma cells.

D. Monstrous abnormal plasma cell (X 600) in aspirated sternal marrow 2 months after beginning of urethane therapy.

E. Clumped plasma cells with dense cytoplasm and pyknotic nuclei in same specimen as D, (X 600).

Case 2, A. R., Unit No. C-10679. This 47 year old white divorced mill worker was referred to Duke Hospital by Dr. A. J. Tannenbaum of Greensboro on October 13, 1947. Her general health had been good until about two years previously when following a marital rift she developed malaise, lost her appetite and became habitually worrisome. Cramps and pains about her muscles and joints developed during the
following months. In March, 1946, she found that her weight was ten pounds below her average. An anemia with blood values about 50 per cent of normal was discovered and it was thought that she improved for a time with vitamin and liver therapy. Two or three months before her hospital admission, she became more or less constantly uncomfortable due to sharp 'stabbing' pains, particularly about her shoulders and trunk. Her family physician after admitting her to a local hospital found that she had fever, anemia, albuminuria and skeletal decalcification. Two blood transfusions were given. Multiple myeloma was considered as a diagnosis but since Bence-Jones protein could not be found in the urine a tentative diagnosis of hyperparathyroidism was made.

Physical examination showed the patient to be a poorly nourished, chronically ill middle-aged white woman. Pressure over the lower ribs was painful. The liver edge was palpable just below the costal margin. There were no enlarged lymph nodes or tumor masses.

Examination of the peripheral blood showed a normochromic, normocytic anemia (table 2). There was marked rouleau formation in the blood films. There was a large amount of protein in the urine and on some occasions a small amount of Bence-Jones protein could be demonstrated. Serologic tests for syphilis were negative. The serum proteins were 8 Gm. per 100 cc., with albumin 2.5 Gm. and globulin 5.3 Gm. The blood calcium was 9.1 mg. per 100 cc., phosphorous 3.8 Gm. and the alkaline phosphatase 1.7 Bodansky units. A bromsulfalein test of liver function, using 5 mg. of the dye per kilogram of body weight, showed 10 per cent retention after 45 minutes. A phenolsulphothalein test of renal function...
showed an excretion of 40 per cent of the dye in two hours. Roentgen examination of the skeleton (fig. 2, A) showed generalized, punched-out destructive lesions in the skull, ribs, scapulae, spine and pelvis. There were questionable areas of bony destruction in the upper end of the right tibia. There was no collapse of the vertebrae. Bone marrow was obtained by aspiration from the sternum and from the spinous process of a lumbar vertebra. Thirty-five per cent of the marrow cells were immature and abnormal plasma cells (fig. 2, C).

**FIG. 2. CASE 2., A. R., UNIT NO. C-19679**

A. Roentgenograms of skull showing multiple small areas of bony destruction before treatment.

B. Repeat roentgenogram seven months after beginning of treatment showing no progression in lesions.

C. Photograph of aspirated bone marrow (X 600) before treatment showing 35% atypical plasma cells.

D. Photograph of clumped plasma cells in aspirated marrow three months after beginning of urethane. Plasma cells were reduced to 4%, with variation in size and altered staining reaction.

The administration of urethane was started on October 20, 1947, giving 4 Gm. per day by mouth. She tolerated it well. On the fourth day of therapy a leukocytosis of 15,900 occurred but during the next month the WBC gradually fell to hover around 4,000. During her two weeks in the hospital, she had a daily rise in temperature to 38–40.2 C. At the end of this time bone pain was decreasing, she had begun to gain weight, and was able to return home. She was seen thereafter at frequent intervals for check up examinations. After a few more weeks her temperature remained normal. Her blood values improved progressively (table 2). The urethane was discontinued after two months of continuous therapy when a total dose of 2.40 Gm. had been given. Re-examination of the bone marrow three months after the beginning of therapy showed that the plasma cells were reduced to 7 per cent. The remaining marrow elements were not notably abnormal.
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Seven months after the start of treatment she had gained 20 pounds in weight. She considered her general health better than it had been for several years. She was able to do all of her work at home except the heaviest tasks. Physical examination at this time showed no abnormalities. Bence-Jones protein could not be demonstrated in the urine. The serum proteins were 8.8 Gm. per 100 cc. as before but the albumin was now 4.4 Gm. and the globulin 3.6 Gm. (table 5). Repeat x-ray films of the skull showed that there had been no progression in the bony lesions. Multiple areas of rarefaction remained (fig. 1, B). Bone marrow was aspirated from the sternum for the third time. The cellularity was within range of normal with a total white cell count of 312,000. Four per cent of the cells were plasma cells. These varied in size to an unusual degree, from about 10 to 50 microns in diameter (fig. 1, D). Their cytoplasm was somewhat indefinite as to boundary and their staining reaction varied from dark to pale blue from cell to cell. Basophilic granulation was not present. The nuclear chromatin stained densely and occurred in coarse clumps. The appearance and distribution of the remaining marrow elements was not abnormal.

A check-up examination at eight months showed no essential changes. She had returned to full time work in a hosiery mill. The blood values had continued to improve (table 2). The urine contained a trace of Bence-Jones protein. A phenolsulphophalein test showed an excretion of 35 per cent of the dye in two hours. The alkaline phosphatase activity had become slightly elevated.

A few weeks later she felt feverish for a day or two. Examination showed more Bence-Jones protein in the urine and an increased number of plasma cells in the bone marrow. She was given 110 Gm. of urethane in a month's time. On a check-up examination thirteen months after urethane therapy was first begun she was working full-time and there was no evidence of further relapse.

Case 3, S. J. C., Unit No. C-28643. This 54 year old electrician was admitted to Duke Hospital on February 23, 1948, for the investigation of anemia, suspected heart and renal disease. He had been well and working regularly until four weeks previously when within a period of a few days he became weak, pale and unable to exert himself physically without becoming short of breath. He had pain about the lower

### Table 3.—Case 3, S. J. C., C-28643, Hematologic Findings

<table>
<thead>
<tr>
<th>Date</th>
<th>Hgb.</th>
<th>RBC</th>
<th>WBC</th>
<th>Hemato-</th>
<th>Reticulo-</th>
<th>Plate-</th>
<th>Differential WBC and therapy</th>
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<tr>
<td></td>
<td>Gm. per 100 cc.</td>
<td>mill. per c.mm.</td>
<td></td>
<td>crit</td>
<td>cytes</td>
<td>lets</td>
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<td>2/14</td>
<td>7.2</td>
<td>2.3</td>
<td>5000</td>
<td>21</td>
<td>4.0</td>
<td>214</td>
<td>Neutrophils 60, stabl 4, metamyelocytes 2, myelocytes 1, promyelocytes 2, lymphocytes 26, monocytes 4, normoblasts 4/100 WBC.</td>
</tr>
<tr>
<td>3/3</td>
<td>6.9</td>
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<td>4450</td>
<td>10</td>
<td>3.4</td>
<td>880</td>
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</tr>
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<td>3.2</td>
<td>925</td>
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<td>24</td>
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<td>3650</td>
<td>27</td>
<td>3.0</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>4/15</td>
<td>9.0</td>
<td>2.7</td>
<td>3200</td>
<td>25</td>
<td>5.0</td>
<td>590</td>
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</tr>
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<td>3600</td>
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<td>7.3</td>
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<td>5/17</td>
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<td>27</td>
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<td>5/28</td>
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<td>3.3</td>
<td>3400</td>
<td>31</td>
<td>2.3</td>
<td>343</td>
<td>Urethane 4 Gm./day</td>
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<td>Urethane 2 Gm./day (268 Gm.)</td>
<td>Neutrophils 72, stabl 4, lymphocytes 14, eosinophils 2, monocytes 8.</td>
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</tr>
</tbody>
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ribs on the right side that was made worse by breathing and coughing. His symptoms became progressively worse. During the week preceding his hospital admission, he was quite drowsy in the afternoons, had little appetite, was often nauseated and vomited once or twice. He found that he slept better at night when using two or three pillows. Early in the morning of the day of his hospital admission he was awakened from sleep by acute dyspnea.

Physical examination disclosed a pale, overweight white male, obviously ill. His blood pressure was 135/80 mm. of mercury. Two small flame shaped hemorrhages were visible near the right optic disc. His heart was slightly enlarged. There was a moderately loud systolic murmur at the apex and the first heart sound was doubled. The liver edge was felt 5 cm. below the right costal margin. The tip of the spleen was palpable. There was slight pitting edema at the ankles.

Laboratory studies showed that he had a severe normochromic, normocytic anemia with immature granulocytes and nucleated red blood cells in the circulating blood (table 3). In fresh and stained films there was conspicuous rouleaux formation. Serologic tests for syphilis were negative. Several urinalyses showed heavy proteinuria and granular casts but no Bence-Jones protein. Blood chemical determinations showed the NPN to be 35 mg. per 100 cc., total proteins 8.5 mg., with albumin 3.8 Gm. per 100 cc. A phenolsulfonphthalein test showed impaired renal function, 5 per cent of the dye appearing in the urine in fifteen minutes and a total of 40 per cent in two hours. The bromsulfalein test of liver function, using 5 mg. of the dye per kilogram of body weight, showed only a trace of the dye remaining in the

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**Fig. 3. Cases 3 and 4**

A. Case 3, S. J. C., Unit No. C-18643. Roentgenogram of skull before treatment showing multiple large and small areas of bony destruction.

B. Case 4, O. M. R., Unit No. C-17783. Roentgenograms of skull showing similar but less extensive bony destruction.

C. and D. Photograph and lateral roentgenogram of myeloma cell tumor of sternum, case 4.
plasma at the end of one hour. An electrocardiogram showed left axis deviation. Roentgen films of the skeleton showed multiple areas of rarefaction in the skull (fig. 3, A) and diffuse demineralization of the vertebrae. Films of the chest showed the heart to be moderately enlarged.

Bone marrow was aspirated from the sternum and from vertebral spinous processes on several occasions. The aspirated marrow was consistently low in cellularity. Sixty-six per cent of the cells were immature, abnormal plasma cells.

Urethane therapy was begun on March 3, 1948. Four grams were given daily in divided doses by mouth. He tolerated the medication well. After eighteen days of therapy, leukopenia developed and the urethane was reduced to 2 Gm. per day. This was continued for sixty-eight days until a total of 172 grams of urethane had been given. There was a slow but progressive rise in the hemoglobin, red blood count and hematocrit (table 3). After completion of treatment, rouleaux formation was no longer present in the blood films. After two months of therapy, the patient thought he felt about as well as he ever had. He had no pain in any region of the body. Three months after the beginning of therapy he was able to return to his regular work without difficulty. A check-up at three and one-half months showed a fall in the hyperglobulinemia. A trace of protein remained in the urine. The NPN was 36 mg. per 100 cc. A PSP test, during which the urine volumes were small, showed a total excretion of 7 per cent of the dye in two hours.

After the urethane had been discontinued for three months, heavy proteinuria reappeared and the blood values fell slightly. Chemical therapy was resumed. Ten months after the beginning of urethane he was working full-time and had no complaints of any kind.

**Case 4, O. W. R., Unit No. C-i7783.** This 51 year old Indian carpenter was referred to Duke Hospital by Dr. G. W. Gunn of Cherokee, N. C. on September 18, 1947. His general health had been good until two years previously when he developed pain in the middle of his sternum. The pain was more or less constantly present during the next few months and, after it had been present for a year, a small nodule de-
veloped. This gradually enlarged and was always very tender. During the four months preceding his hospital visit, he was troubled with nausea and vomiting.

Physical examination showed an undernourished man. In the middle of the sternum, just below the sternal angle, there was a flat, square elevated tumor measuring 5 by 5 cm. (fig. 3, C). There was pain in this area with respiratory and other chest movements. He could not bear pressure on it. There were no other relevant abnormalities.

### Table 5.—Blood Chemical Values in Four Patients with Multiple Myeloma treated with Urethane.

<table>
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<tr>
<th>Date</th>
<th>Serum proteins</th>
<th>Albumin</th>
<th>Globulin</th>
<th>Ca</th>
<th>P</th>
<th>Phosphatase, Bodansky units</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
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* Period of urethane treatment.

Urinalysis showed albuminuria on rare occasions. Examination of the peripheral blood (table 4) showed normal values. Rouleaux formation of the red cells was present in wet preparations and in the stained blood films. Blood chemical determinations were as follows: total proteins 8 Gm. with 2.3 Gm. albumin and 4.8 Gm. globulin, calcium 9.4 mg., phosphorous 4.0 mg. and phosphatase 1.8 Bodansky units per 100 cc. A roentgen film of the chest showed the lungs to be clear. There were areas of rarefaction in the ribs. A fusiform swelling occurred in the mid portion of the sternum (fig. 3, D).

A needle was inserted into the sternal mass. Aspiration yielded cellular material. In the stained films 91 per cent of the cells were young abnormal plasma cells. Bone marrow aspirated from the spinous process of the third lumbar vertebra showed 25 per cent of similar abnormal plasma cells.

Irradiation therapy to a total of 1,050 roentgens was given through 8 by 8 cm. port over the sternal
tumor in October 1947. During the next few months he had far less pain about the sternum but the tumor mass did not decrease in size.

He was recalled for a check-up examination on April 12, 1948. At that time he complained of more pain than on previous occasions, especially when he exerted himself physically. The discomfort was noted particularly over the left upper humerus, about his ribs and sternum. Physical examination showed no obvious changes. Examination of the blood showed that there had been some deterioration in the blood values (table 4). A specimen of bone marrow from a spinous process was again examined and 39 per cent of the cells were abnormal plasma cells. The serum proteins had risen to 10.1 Gm. per 100 cc. with albumin 2.9 Gm. and globulin 7.2 Gm. (table 5). X-ray films of the chest, skull, left humerus and sternum showed little definite extension of the areas of previous bone destruction.

The administration of urethane was started on April 13, 1948, with a dose of 4 Gm. per day by mouth. During the next four weeks, his pain became gradually less except about an area on the lateral chest wall where a rib had apparently been fractured during the maneuvers incident to making roentgen films. Examination of the blood showed that a leukopenia had developed. An increased number of plasma cells was still present in the bone marrow, but they were now larger in size and their cytoplasm more densely stained. Their nuclei were extremely eccentric and the chromatin was aggregated into dense clumps.

The administration of urethane was continued at home under the supervision of his family physician. The leukopenia persisted but became no more severe. Without notable trauma another rib fracture occurred and severe pain developed about one hip. He was admitted to his local hospital and the pain subsided at bed rest.

The urethane was used somewhat irregularly. On a check-up examination three months after the beginning of treatment he considered himself definitely improved. Urethane was discontinued and for two months he was virtually free of symptoms. Skeletal pain then gradually reappeared and he did not return for further treatment. He died at home seven months after the beginning of urethane therapy.

**DISCUSSION**

Multiple myeloma is a malignant disease resulting from the excessive proliferation of abnormal plasma cells within the bone marrow. The clinical course is variable, as judged by the length of survival of individual patients, but uniformly progressive and ultimately fatal. There is no evidence that real spontaneous remissions occur.

Therapy in the past has been unsatisfactory. The commoner agents useful in the treatment of the lymphomatosus diseases, roentgen irradiation, radioactive phosphorous, and nitrogen mustard compounds, have little demonstrable effect beyond relieving pain in some individuals. Stilbamidine, pentamidine, and antimony compounds have been reported to relieve skeletal pain and produce apparently specific granular changes in the cytoplasm of the myeloma cells.

The 4 patients included in this study illustrate many of the variable clinical features of multiple myeloma. In Cases 1 and 3 the disease was rapidly progressive. In the other two it was progressing slowly. Case 4 was thought at first to have a solitary myeloma cell tumor of the sternum. Examination of marrow obtained from other bones showed the disease to be generalized. The major effect of roentgen therapy to the sternal tumor was relief of pain. In Case 1 the predominant feature was a devastating skeletal disease. Metastatic carcinoma was considered a good possibility, as it frequently must be, in the differential diagnosis. In Case 3 symptoms of cardiac failure were precipitated by anemia. The presence of renal disease complicated the diagnostic problem. The finding that the anemia did not result from renal failure, however, and the occurrence of immature granulocytes in the circulating blood led to a bone marrow examination and the discovery of plasma...
cell overgrowth. There was no skeletal pain and roentgen films showed significant abnormalities only in the skull. In all patients the crucial diagnostic information was provided by examination of the bone marrow.

The treatment adopted in these cases was entirely empiric. The urethane was given in divided doses by mouth in the form of an elixir or syrup. All four of the patients tolerated the chemical exceptionally well with virtually no gastrointestinal symptoms. During the first three to four weeks they were given 4-6 Gm. per day. Three patients developed leukopenia following which the dose was reduced to about 2 Gm. daily or temporarily suspended. Further fall in the white cell count did not occur. The urethane was given over a period of about two months and then discontinued. The total dose per patient varied from 120-240 Gm. Treatment and post-treatment periods of observation ranged from seven to thirteen months. Two patients relapsed and were given a second course of therapy.

All 4 patients showed much the same type of response to urethane. General clinical improvement appeared during the second and third week of therapy when skeletal pain and fever began to subside. Physical activity soon became tolerable within the obvious limitations imposed by skeletal disease. The two patients with most extensive areas of skeletal destruction were able to perform ordinary activities and do light work within four to six months of the start of treatment without discomfort.

A normochromic, normocytic anemia with hemoglobin values ranging from 7.2 to 11.0 Gm. was present in all 4 patients. In 2 cases, immature granulocytes and nucleated red cells were present in the circulating blood. An abrupt but transient leukocytosis was noted in 2 patients on the fourth day of urethane administration, possibly the result of chemical stimulation of cell division. Leukopenia with white cell counts ranging between 2,600 and 4,400 developed in about three to four weeks. Reduction in the urethane dosage to around 2 Gm. per day was sufficient to prevent the development of more serious white cell depression. In about the same time evidence of marrow crowding subsided, immature granulocytes and nucleated red blood cells disappearing from the circulating blood. Progressive fall in hemoglobin and red cell values ceased after one to two weeks of urethane but notable regeneration of blood did not begin before four to six weeks. There was gradual improvement in the blood values toward normal for several weeks following the termination of urethane therapy.

The initial bone marrow aspiration showed in all cases the massive proliferation of abnormal plasma or "myeloma" cells diagnostic of multiple myeloma. Repeated examinations of bone marrow in Cases 1, 2, and 3 obtained from different sites after urethane therapy revealed a striking quantitative decrease in the number of these cells. A characteristic change in myeloma cell morphology occurred, also, with urethane administration. Some became monstrous in size, recalling the changes observed in plant seedlings. Others as observed in spread films made from aspirated marrow tended to adhere together in small compact clumps. Variation in cell size, densely staining cytoplasm, and eccentric and pyknotic nuclei were general features of those myeloma cells which persisted after urethane administration. Basophilic granulation of the cytoplasm did not develop.
The initial blood chemical values (table 5) were typical of those occurring in multiple myeloma. In Case 1, the serum calcium was elevated to 12.4 mg. per 100 cc., but in all other instances it was normal. Phosphatase activity, determined in 3 cases before treatment, was low or normal and in 2 patients with extensive skeletal disease it increased slightly after urethane administration.

Hyperglobulinemia with reversal of the albumin globulin ratio was present initially in all cases. In Cases 1, 2, and 3 the serum globulin fell markedly and the albumin rose slightly to restore a normal ratio of these protein components during the period of after treatment follow-up. The serum proteins were studied electrophoretically in these 3 cases before and after urethane treatment, and will be reported in detail later by Dillon and Rundles. The total protein showed the electrophoretic mobility of gamma globulin. Four months after the beginning of urethane therapy protein with this mobility was reduced to 18.0 per cent. In Case 2, a similar increase in the gamma globulin occurred, amounting to 45.7 per cent of the total. Seven months after urethane administration was begun this component was reduced to 23.8 per cent. In Case 3, the initial electrophoretic study showed that the abnormal protein had a boundary lying between the beta and gamma globulins, the M variety of protein abnormality in multiple myeloma described by Gutman, et al. The total percentage of M and gamma globulins before treatment totaled 45.2 per cent. Three and one-half months later these fractions had fallen to 33.4 per cent.

Renal disease as evidenced by proteinuria of greater or less degree was present in all of the patients with multiple myeloma. Bence-Jones protein was demonstrated in the urine of two. None had nitrogen retention. The excretion of phenolsulphonphthalein dye was impaired in two patients before treatment was started. During the weeks following urethane administration nitrogen retention did not develop, albuminuria tended to subside and Bence-Jones proteinuria was less often demonstrable.

Serial roentgen films taken over a period of months following urethane therapy showed no progression in the destructive skeletal lesions which are so prominent a feature of multiple myeloma. The subsidence of bone pain occurring at bed rest, followed in a few weeks by the ability to tolerate moderate physical activity, suggested improvement in skeletal support as a result of therapy. The slight increase in phosphatase activity suggests some attempt at bony repair. There was definite roentgen evidence of recalcification in one patient 6 months after the beginning of treatment. Bony softening persists without doubt for some period of time, and perhaps indefinitely. Roentgen films of the skeleton thus provide no means for judging the early response to therapy, but the chronicity of the lesions does caution against the too rapid expansion of physical activity.

Evidence has been presented to show that the administration of urethane to patients with multiple myeloma alters the fundamental abnormalities of the disease in a selective and beneficial way not possible by previously available therapeutic agents. The present report concerns only the early responses to treatment. The long term results remain to be studied. At this time we have no doubt that urethane therapy has already prolonged life in 2 cases in whom the disease was
rapidly progressive. Relapses of the disease may not occur for as long as six months or longer after discontinuation of therapy. Whether interrupted or continuous therapy will eventually prove most desirable is a matter of conjecture. To detect reactivation of the disease so that therapy can be given again when indicated will require serial blood examinations, frequently repeated bone marrow studies with attention to the number and appearance of the plasma cells, quantitative study of proteinuria, and serial studies of the serum proteins preferably by electrophoretic methods. The effect of urethane therapy offers a new tool in investigating the complex protein and cellular abnormalities which characterize the disease.

CONCLUSIONS

Four patients with multiple myeloma have been treated with urethane (ethyl carbamate) for eight to ten weeks in total doses of 120–190 Gm. and observed over periods ranging from seven to thirteen months. Striking benefit relating to all aspects of the disease was observed. Fever, skeletal pain and acute symptoms subsided after two to four weeks of therapy. In individuals with severe anemia, immature granulocytes and nucleated red cells disappeared from the circulating blood, and over a period of several weeks, the blood values improved greatly toward normal. Abnormal plasma or “myeloma” cells decreased quantitatively in the bone marrow and underwent morphologic changes indicative of retarded or arrested growth. The serum protein abnormalities characteristic of multiple myeloma became less pronounced or disappeared as did the albuminuria and Bence-Jones proteinuria. Serial roentgenograms of the skeleton showed no progression in the destructive lesions. There was little evidence of skeletal recalcification, however, for four to six months after treatment. The long term results of urethane therapy in multiple myeloma, the liability to exacerbation of the disease, the effectiveness of subsequent courses of urethane therapy, the course of the associated renal disease, the extent of skeletal recalcification and repair, etc., are matters for further study.

REFERENCES

URETHANE THERAPY IN MULTIPLE MYELOMA

2.16


URETHANE (ETHYL CARBAMATE) THERAPY IN MULTIPLE MYELOMA

J. PHILIP LOGE and R. WAYNE RUNDLES