A Controlled Trial of Urethane Treatment in Multiple Myeloma


Urethane has been employed in the treatment of patients with multiple myeloma for nearly two decades.\textsuperscript{1,2} Relief of bone pain, increases in hemoglobin concentration, and decreases in serum and urinary protein concentrations have been reported in patients so treated.\textsuperscript{1,5} Despite the extensive observation period, however, there is no consensus concerning the effects of urethane on objective parameters of the neoplastic activity,\textsuperscript{6} and significant prolongation of survival of patients with multiple myeloma treated with urethane has not been shown.\textsuperscript{7}

A clinical trial was therefore planned and executed from June 1958 to March 1961 by a group of cooperating physicians.\textsuperscript{8} This study was designed to determine if the inclusion of urethane in a program of optimal medical care for myeloma produced results different from an identical regimen in which a placebo solution was administered. The treatment was given and results evaluated without deciphering the drug code, in an effort to avoid bias. The results of the trial in 83 patients with multiple myeloma, together

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*Eastern Solid Tumor Group of the Cancer Chemotherapy National Service Center.
with observations on the course of the disease, constitute the basis of this report.

**MATERIALS AND METHODS**

Patients were studied in six institutions in accordance with a detailed written experimental design.* All patients admitted to the trial had an unequivocal diagnosis of multiple myeloma. The several diagnostic parameters used were (a) greater than 10 per cent myeloma or plasma cells in a marrow aspirate in the presence of clinical disease compatible with myeloma; (b) a measurable soft tissue tumor in a patient with biopsy-proved myeloma; (c) the presence of "M" protein by electrophoresis of serum; (d) "M" protein demonstrable by electrophoresis of urine; (e) osteolytic lesions (generalized osteoporosis also qualified if marrow plasmacytosis was greater than 30 per cent in the presence of clinical disease compatible with the diagnosis) or (f) plasma cells in two or more smears of peripheral blood. In order to qualify for the study, patients were required to fulfill diagnostic requirements (a) or (b) plus at least one of (c), (d), (e) or (f).

Patients were accepted for study irrespective of the blood urea nitrogen concentration. Neutropenia or thrombocytopenia from prior treatment delayed entry into the study until levels were repeatedly in excess of 1000/cu. mm. or 75,000/cu. mm., respectively. To avoid confusion of therapeutic and toxic effects in those patients who had previously been treated with urethane or an alkylating agent, a minimum period of 30 days after cessation was required before entry into the study. Localized x-ray treatment or corticosteroid administration delayed entry for only 15 days after cessation.

Each patient was assigned to one of three groups, dependent on his prior treatment history: (a) prior urethane; (b) other prior treatments for myeloma—e.g., corticosteroids, alkylating agents, radiotherapy, etc.; and (c) no prior therapy for myeloma. Treatment with urethane or placebo syrup was allocated at random within each group by directions in sealed opaque envelopes. The solutions were prepared in several batches throughout the study by the same research pharmacist† and were physically indistinguishable. Analytic reagent grade urethane was used. Each syrup contained identical flavoring agents, including 200 mg./L. of quinine for bitter aftertaste, in an attempt to eliminate inadvertant code break by distaste for urethane. Cherry- and cola-flavored syrups were made in both urethane and placebo preparations to allow shift of medication flavor within code in an attempt to achieve maximal drug administration. Syrup was administered in 10 ml. aliquots from calibrated medicine glasses. The urethane solution contained 1 Gm. of urethane per 10 ml. The dose was increased daily until 10 ml. 4 times daily was ingested, which provided a maximal urethane dose of 4.0 Gm./day. If substantial alimentary intolerance occurred, reduction of dose and subsequent readjustment to the highest tolerated level was accomplished. Clinical and laboratory appraisals were obtained at specified frequent intervals. Granulocytopenia less than 1000, thrombocytopenia less than 75,000, and other hazardous clinical situations reasonably attributable to the drug were the basis for temporary withdrawal of drug, and subsequent readjustment to maximum dose tolerated.

Optimal medical care included appropriate therapy of infections and use of orthopedic appliances, analgesics, blood transfusions and antiemetics. Localized irradiation was used only for intolerable pain or incipient spinal cord compression. Extensive irradiation or other experimental chemotherapeutic compounds were not permitted. Hormonal treatments were similarly prohibited excepting prednisolone, which was used only for advancing azotemia, thrombocytopenia with bleeding, hypercalcemia, or life-threatening illness, at a dose of 1.5 mg./Kg./day orally or parenterally in divided doses. Rapid

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*We are grateful for the helpful suggestions of Dr. R. Wayne Rundles, Durham, N. C., in the design of this protocol.

†We are indebted to Mr. Robert Case, Roswell Park Memorial Institute, for this service.
tapering of doses with standardized corticotropin administration was also called for to minimize any time on corticosteroids.

Treatment was designed to be administered for a minimum of 16 weeks, and longer if a therapeutic effect was noted. The senior investigator at each institution could exercise the prerogative of shortening the study period if toxicity, despite dose adjustments, was deemed clinically unacceptable or hazardous to the patient.

RESULTS

Eighty-three patients entered the study. Their prior therapeutic experience and allocation to treatment is shown in table 1.

Only 16 of the 83 patients had had prior urethane treatment, and they are proportionately distributed to each treatment.

In table 2 it can be seen that the median ages of the groups, subclassified by prior treatment experience, are similar. The sex distribution is unequal in patients who had had prior treatment other than urethane. The median times from symptomatic onset to diagnosis were comparable within each group. Ten patients in the whole group had symptoms for periods in excess of 1 year before diagnosis; the maximum was 4 years. The median duration of disease from diagnosis to onset of study reflects in part the time in treatment for subgroups A and B.

Evidence of extent and severity of disease are presented in table 3. Nearly every patient had osteolytic skeletal lesions. Median marrow content of plasma cells or myeloma cells was comparable for placebo and urethane groups except within groups (A) previously treated with urethane. The mean serum protein concentrations for the subgroup were also similar except for groups A, where the random allocation has resulted in a lower concentration for the placebo group. It appears in group A that high marrow plasma cell contents might be associated with high serum protein values, and vice versa. When these two parameters were studied for the entire group by appropriate graphic plots, however, no correlation was found between plasma cell content of marrow and total protein or "M" protein concentration. Immunoelectrophoretic classification of proteins was not performed. The mean hemoglobin concentrations for all groups were similar and clearly in the anemic range. The mean leukocyte counts were normal. Three-fourths of patients had proteinuria. Bence-Jones proteinuria was detected in only 17 patients.

There were 40 patients with azotemia at the outset of study. The random allocation produced a sharp difference in their distribution between urethane and placebo treatments in group A.

The planned treatment course often was not completed. A major difference in patients' tolerance of the treatment syrups is reflected in median total doses and durations of treatments (table 4). Whereas 25 of 36 placebo patients received drug for 8 weeks or more, only 18 of 47 urethane-treated patients did so.

Hematologic evidence of drug effect is perhaps the best measure of the adequacy of urethane dosage. In table 5 the effects of urethane and placebo on leukocyte counts are compared. The mean of the lowest counts for each patient during treatment is lower in the urethane group than the placebo. The
Table 1.—*Therapeutic History and Treatment Allocation of 83 Patients with Multiple Myeloma*

<table>
<thead>
<tr>
<th></th>
<th>Urethane</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = Prior urethane</td>
<td>9</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>B = Prior treatments, other</td>
<td>23</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>C = No prior treatment</td>
<td>15</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>All patients</td>
<td>47</td>
<td>36</td>
<td>83</td>
</tr>
</tbody>
</table>

Table 2.—*Median Age, Sex Distribution, and Median Duration of Disease from Diagnosis to Onset of Study in 83 Patients with Myeloma*

<table>
<thead>
<tr>
<th>Subgroup*</th>
<th>Urethane Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs.</td>
<td>61 59 60 62</td>
<td>60 60 61 60</td>
</tr>
<tr>
<td>Sex distribution, male/total, per cent</td>
<td>53 44 52 60</td>
<td>72 43 93 67</td>
</tr>
<tr>
<td>Median time, months, symptoms to diagnosis</td>
<td>3 1 5 4</td>
<td>4.5 2.5 5 2.5</td>
</tr>
<tr>
<td>Median duration of disease, months, from diagnosis to onset of study</td>
<td>2 2 7 1</td>
<td>2 7 3.5 1</td>
</tr>
</tbody>
</table>

*A = prior urethane; B = other prior treatment; C = no prior treatment of myeloma.

mean lowest leukocyte count in the placebo group appeared to represent isolated values and thus might be misleading. Indeed, when all leukocyte counts in the last half of each patient's treatment period were averaged, the counts on patients receiving placebo were found to be normal. The urethane-treated patients who took 100 Gm. or more of drug had definite leukopenia. One-third of the urethane patients had one or more leukocyte counts less than 2,000/cu. mm.

In table 6 those objective parameters are shown where some improvement was seen. Decrease in marrow plasma cells occurred more frequently in urethane-treated patients, but if account is taken of the five patients who had subsequent fluctuations back to higher levels during the study, this appears to be of little consequence. A fall in total serum protein of 2 Gm. per cent or more occurred in six placebo-treated patients, and an equal proportion of urethane-treated patients. This was not due exclusively to a fall in M protein. Only one patient, in the placebo group, experienced sustained fall in urinary protein excretion. Spontaneous rise in hemoglobin or decrease in transfusion requirement were more frequent in the placebo group. Important symptomatic benefit was defined as improvement in the performance status* by an amount of 2 levels or more. Five instances were seen in the urethane group, and seven in the placebo-treated patients. In four instances in each treatment group the improvement was independent of recent transfusion. Eight placebo-treated and eight urethane-treated patients received prednisolone at

*0—No impairment of normal performance; 1, 2, 3—mild, moderate, severe impairment; 4—moribund.
Table 3.—Initial Laboratory Findings in 83 Patients with Myeloma

<table>
<thead>
<tr>
<th>Extent of Disease</th>
<th>Urethane</th>
<th></th>
<th></th>
<th>Placebo</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>Total</td>
<td>A</td>
</tr>
<tr>
<td>Total patients</td>
<td>47</td>
<td>9</td>
<td>23</td>
<td>15</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Number of patients with skeletal lesions</td>
<td>40(x)</td>
<td>8</td>
<td>20(x)</td>
<td>12(x)</td>
<td>34(y)</td>
<td>6(x)</td>
</tr>
<tr>
<td>Plasma cells in marrow, median</td>
<td>23.4(x)</td>
<td>50%*</td>
<td>26%*</td>
<td>23%*</td>
<td>25%*</td>
<td>11%*</td>
</tr>
<tr>
<td>Total protein, Gm. per cent, mean(\Delta)</td>
<td>8.5 ± 2.4</td>
<td>9.8 ± 1.7</td>
<td>8.5 ± 2.7</td>
<td>8.3 ± 2.2</td>
<td>8.5 ± 2.5</td>
<td>7.2 ± 2.0</td>
</tr>
<tr>
<td>Hgb. Gm. per cent mean(\Delta)</td>
<td>9.2 ± 1.8</td>
<td>9.3 ± 1.1</td>
<td>8.9 ± 2.2</td>
<td>9.8 ± 1.8</td>
<td>9.5 ± 1.4</td>
<td>10.0 ± 1.4</td>
</tr>
<tr>
<td>Leukocytes × 10(^9)/cu. mm., mean(\Delta)</td>
<td>6.5 ± 4.2</td>
<td>6.0 ± 4.4</td>
<td>5.4 ± 2.2</td>
<td>8.5 ± 5.6</td>
<td>5.9 ± 2.0</td>
<td>5.6 ± 3.1</td>
</tr>
<tr>
<td>Patients with proteinuria</td>
<td>34(x)</td>
<td>7(y)</td>
<td>16(z)</td>
<td>11(z)</td>
<td>27(y)</td>
<td>5(x)</td>
</tr>
<tr>
<td>Patients with Bence-Jones proteinuria</td>
<td>9(x)</td>
<td>3(x)</td>
<td>3(v)</td>
<td>3(v)</td>
<td>8(x)</td>
<td>2</td>
</tr>
<tr>
<td>Number of patients with azotemia(\ast)</td>
<td>23(x)</td>
<td>6</td>
<td>11(x)</td>
<td>6</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

\(x = 1\) patient not reported.
\(y = 2\) patients not reported.
\(z = 3\) patients not reported.
\(v = 5\) patients not reported.
\(\Delta = \pm 1\) S.D.
\(\ast = \) Mean urethane A = 44 per cent. Mean placebo A = 13 per cent.
\(\ast = \) In 69 of the 83 patients an M spike or increase of \(\gamma\) globulin was described.
\(\ast = \) Blood urea nitrogen equal to or greater than 20 mg. per cent, serum urea nitrogen equal to or greater than 15 mg. per cent, or non-protein nitrogen equal to or greater than 40 mg. per cent.
some time during the study. Two of the improvements described, one hemoglobin rise and one reduction in transfusion requirement, were associated with prednisolone administration, although its role in their causation cannot be clearly defined. The prednisolone effect in the objective modification of myeloma, two improvements in 16 patients, was thus not striking. Five ure-
Table 6.—Beneficial Effects

<table>
<thead>
<tr>
<th></th>
<th>Urethane</th>
<th></th>
<th></th>
<th>Placebo</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total A</td>
<td>B</td>
<td>C</td>
<td>Total A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>47</td>
<td>9</td>
<td>23</td>
<td>15</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Decrease in plasma cells ≥ 8%</td>
<td>11ab</td>
<td>1</td>
<td>6a</td>
<td>4b</td>
<td>8bc</td>
<td>2c</td>
</tr>
<tr>
<td>Decrease in plasma cells ≥ 20%</td>
<td>6b</td>
<td>1</td>
<td>4b</td>
<td>1</td>
<td>4c</td>
<td>1c</td>
</tr>
<tr>
<td>Decrease in serum protein</td>
<td>≥ 2 Gm.</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Decrease in “M” protein ≥ 25%</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Increase Hgb. without Tx</td>
<td>≥ 2 Gm.</td>
<td>2d</td>
<td>0</td>
<td>2d</td>
<td>0</td>
<td>4de</td>
</tr>
<tr>
<td>Transfusion requirement reduced by 1000 ml./mo. in the second month</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1d</td>
<td>1d</td>
</tr>
<tr>
<td>Performance rate improved by 2 levels*</td>
<td>5f</td>
<td>0</td>
<td>4f</td>
<td>1</td>
<td>7fg</td>
<td>1</td>
</tr>
<tr>
<td>Sustained decrease in urinary protein by 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Change in Bence-Jones proteinuria positive to negative</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3f</td>
<td>1</td>
</tr>
<tr>
<td>Bone healing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* = Transient in 3 patients.  
b = Transient in 2 patients.  
c = Transient in one patient.  
d = One patient was receiving prednisolone and antibiotics.  
e = One patient received x-ray treatment prior to Hgb rise.  
f = One patient received transfusion just prior to performance change.  
g = Two patients received transfusion just prior to performance change.  
0 = No impairment of normal performance; 4 = moribund.

thene-treated and eight placebo-treated patients required radiotherapy during the study.

A total of 77 beneficial effects are seen in table 6. Fifteen patients qualified for two benefits and four additional patients qualified for three benefits each. The records of these 19 patients showing two or more parameters of improvement (11 received urethane; eight received placebo) were especially scrutinized to determine if there was overall clinical improvement that could reasonably be accepted as therapeutic effect. This analysis was performed while the drug identity was still coded. In 11 instances the benefits represented posttransfusional improvement or laboratory changes only. In the remaining eight patients (four patients in the urethane group and four who received placebo), although some clinical change took place, the response was considered of important therapeutic effect or duration in only one urethane-treated patient, and in that instance it was associated with asymptomatic advancing osteolysis. In one urethane-treated patient, benefit was associated with clearing of infection by antibiotics and the use of prednisolone; in two placebo-treated patients x-ray treatment and control of infection, respectively, preceded benefit. Bone healing was seen on one occasion only, in a placebo-treated patient.

Since evidence of objective improvement which might clearly distinguish between urethane- and placebo-treated patients was not found, we examined
survival as an overall assessment of drug effect on the patient and his tumor. The survival for urethane-treated myeloma patients plotted by the life table method is less than that for patients treated with optimal medical care and a placebo (fig. 1). The apparent difference in the 2 treatments occurs in the first 3 months, when nearly 40 per cent of the urethane-treated patients die, compared to 25 per cent of the placebo-treated patients. The apparent proximate causes of death are similar in the 2 treatment regimens except for one instance of coma possibly ascribable to urethane. After 3 months, the curves have essentially the same relative slopes. The shorter median life span in the urethane group was seen in all 3 categories independent of treatment history (table 7).

If the urethane-treated group systematically started treatment later in the course of their disease, by some flaw in randomization such a curve might result and falsely implicate the drug in the curtailed survival. This does not appear to be the case. Figure 2 shows the survival time from symptoms to death related to treatment experience, and again urethane treatment was characterized by somewhat shorter survival. The medians for both groups are well within those of previously reported experience.7

An examination of the records of each patient who died in the first 3 months revealed that azotemia at death was more commonly a factor in early mortality of patients who were previously untreated (ten), than in previously treated patients (two) (table 8). This suggests that the population of previously treated patients is favorably selected for the present study by the exclusion of patients already dead early from renal disease. Leukopenia to half the starting level or less occurred in nine of the 19 urethane-treated patients, and thrombocytopenia of similar degree in 7, including three who also had leukopenia. Hematologic toxicity occurred independently of severe azotemia, suggesting it was not conditioned by impaired renal function. In nine placebo-treated patients who died within 3 months, three instances of thrombocytopenia, one with leukopenia, occurred.
Table 7.—Median Survival from Onset of Treatment of Patients with Multiple as Influenced by Prior and Present Treatment

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethane</td>
<td>8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td>10.5</td>
<td>12</td>
</tr>
</tbody>
</table>

A = Prior urethane.
B = Other prior treatment.
C = No prior treatment.

A survival curve was plotted by the life table method in which patients were grouped by renal functional status and treatment category (fig. 3). If, at any time during observation, there was evidence of azotemia, defined as BUN > 20 mg. per cent, serum UN > 15 mg. per cent, or NPN > 40 mg. per cent, the patient was analyzed as an azotemic. The survival of placebo-treated and urethane-treated nonazotemic patients was similar. The azotemic patients treated with placebo medication survived nearly as long as patients without azotemia. The urethane-treated azotemic patients, however, had recognizably shorter survival, with a median of 2.5 months.

The major characteristics which might affect survival were analyzed in the patients of groups B and C who had never had urethane previously. No influence of age, sex or total protein concentration was found. Because hemoglobin concentration, marrow plasma cell content, azotemia and performance status were individually suggestively related to survival, a composite index was devised. The rank order among the determinations made on patients in groups B and C at onset of treatment was determined for each of the four parameters. The sum of each patient’s four ranks became his selecting index. The median survival for the top middle and bottom index groups of urethane- and placebo-treated patients were then determined. These data are shown in table 9.

The hypothesis that the risk of death at any point in time is the same for urethane- and placebo-treated patients is improbable for the middle and bottom thirds of the index. Indeed in the worst two-thirds of both B and C, urethane does worse than placebo (p < .05). In the top third there is no demonstrated superiority for either treatment (p > .95). Thus, though urethane may exact a significant toll in patients with poor prognostic index, there was no redeeming advantage from its use even in the patients who started with the top third prognostic index. Three of the nine patients (table 4) who received more than 400 Gm. of urethane were represented in the top third.

It is of note that survival of patients previously untreated (in group C) and treated with placebo significantly correlates with prognostic thirds (p < .02), whereas survival in group B is less strongly related to the prognostic indexes (p > .6). The weaker relationship among previously treated patients (group B) may represent selection of the group by deaths during treatments other than urethane, with only the hardier survivors reaching this study.

The frequency of bilirubinemia in excess of 1.5 mg. per cent, appearing
during the treatment period was studied, since urethane has been described as an hepatotoxin in man. Two instances were seen in the placebo group, whereas four were found in the urethane-treated patients. In one previously untreated patient who received 137 treatment days of urethane, central hepatic necrosis was the principal cause of death.

**DISCUSSION**

The method of the controlled clinical trial with coded drugs and placebo is well suited to investigate the fundamental question posed: Does the inclusion of urethane in a program of optimal medical care produce therapeutic results in patients with multiple myeloma superior to an identical regimen without urethane? The mechanics of the study allowed patients to be subclassified by prior therapeutic exposure: urethane, treatment other than urethane, and no prior treatment. Among patients previously exposed to urethane, the apparently healthier ones, despite random allocation, were predominant in the placebo treatment regimen (tables 3 and 7).

Drug coding was relatively imperfect in the present study because the placebo solution, despite its identical color and additional flavoring agents, did not faithfully reproduce the taste, emesis and profound anorexia caused by the urethane solution. The median dose of the urethane solution ingested was less than half that of the placebo solution (table 4). Only 14 of the 38 patients who had never had urethane previously were treated with urethane for 8 weeks or longer. This abbreviation of the planned course was explained either by death or by toxicity sufficiently severe in the view of the senior investigator in each institution to require termination of the study. The duration of treatment in each institution was similar, suggesting that the assessment of drug tolerance was relatively uniform among the several senior investigators.

The hematologic depressive effects of urethane solution were readily recognizable in patients who received in excess of 100 gm. of urethane. The
mean nadir of leukocyte count was approximately 2500/cu. mm. and 15 of 47 urethane-treated patients attained leukocyte counts less than 2000/cu. mm. When the placebo group was studied, the mean lowest count was approximately 3700/cu. mm. Since this leukocyte depression was unexpected, further search was made to determine if it represented a trend toward leukopenia in the placebo-treated (natural) course of multiple myeloma. When all leukocyte counts obtained on each patient in the second half of his treatment with placebo solution were averaged, however, no leukopenia was found, and no important change is seen from the leukocyte count at the outset of study. The leukopenia in the urethane group is real, however, and the mean of all counts in the last half of each patient's treatment period is 4400 (table 5). This leukopenia due to urethane offered another possibility of deciphering the drug code. The effect of urethane on one host system, maintenance of the peripheral leukocyte count, attests that the drug was given in biologically active doses. Thirteen of 28 patients who received more than 100 Gm. had a fall in leukocytes to below 2000/cu. mm., although it was transient.

None of the parameters indicative of clinical activity of myeloma was improved to a significantly greater extent in the urethane treatment group than in the placebo group (table 6). Differences in apparent plasma cell infiltration in marrow were at times extreme, supporting the proposition that isolated determinations may be nonrepresentative and perhaps deceptive. There is an association of urethane administration and earlier death in patients who were or who became azotemic, which approaches significance but might have occurred by chance (p = .17). This suggests that renal excretory or detoxification mechanisms may play a larger role in the human metabolism of urethane than is presently recognized. No greater frequency of leukopenia or thrombocytopenia was found in the azotemic patients who died within 3 months, however, than in nonazotemic patients who died in this period.

The failure to demonstrate significant chemotherapeutic activity for ure-
urethane, when contrasted to a placebo treatment group concomitantly studied, should urge caution in accepting many of the therapeutic claims advanced for urethane in multiple myeloma. It may be that some of these claims derive from minor objective changes, or symptomatic improvements which in the clinical methods of this group would qualify for a change in performance status of only one level.

There are, however, several detailed published case records of objective improvements in multiple myeloma during urethane administration, which appear incontestable. Some, but not all, of these reported patients received larger drug doses than were used in the management of patients in this study. The failure of several experienced clinical investigators in a number of institutions to be able to administer chemotherapeutic doses of oral urethane syrup is evidence of its lack of impressive selective toxicity for the tumor.

A refinement of the present data was possible by construction of a prognostic ranking system relative to other patients, not dependent on arbitrary laboratory values. The top third of patients were unaffected by urethane when contrasted to placebo. The worst two-thirds in the prognostic index, when treated with urethane, however, had shorter survival than placebo-treated patients (< .05).

After the present data were accumulated, a study was undertaken by Seibert et al. in which 0.2 Gm./Kg. urethane was administered by infusion 3 times weekly to patients with myeloma in courses adjusted to peripheral leukocyte count and other toxicity. Analysis of the data of those investigators according to the same parameters used in this study reveal that 18 of 30 patients sustained leukopenia of 2000/cu. mm. or less. Using the criteria for changes presented in table 6, one of 26 patients showed decrease in serum protein; two of 30 sustained hemoglobin rise unassociated with transfusion; six had plasma cell decreases equal to or greater than 20 per cent, and nine
Table 9.—Median Survival from Onset of Treatment of Patients Not Previously Treated with Urethane as Influenced by a Prognostic Index

<table>
<thead>
<tr>
<th>Prognostic Index</th>
<th>Group B</th>
<th>Placebo</th>
<th>Urethane</th>
<th>Group C</th>
<th>Placebo</th>
<th>Urethane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top third</td>
<td></td>
<td>11</td>
<td>17.5</td>
<td></td>
<td>13+†</td>
<td>19.5</td>
</tr>
<tr>
<td>Middle third</td>
<td></td>
<td>10.5</td>
<td>6</td>
<td></td>
<td>16+†</td>
<td>2.5</td>
</tr>
<tr>
<td>Bottom third</td>
<td></td>
<td>10.5</td>
<td>3.5</td>
<td></td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

B = Other prior treatment (not urethane).
C = No prior treatment.

*The prognostic index included those parameters which individually experienced suggestive influence on survival: hemoglobin concentration, performance status, azotemia, and marrow plasma cell content. See text.

†Medians taken of 4 patients, and calculated between second and third patient. Longest surviving 2 patients in each group are continuing remission or lost to follow-up. Top third 14+, 36+. Middle third 19+ and 47+. Medians shown thus are indefinite.

greater than 8 per cent. Seven of 30 had subjective improvement listed as 2 plus or greater, but in three this was associated with x-ray treatment. Two palpable tumors decreased in size. Four patients appear to have benefited clinically during the treatment. These data are consonant with those of this study, and support the conclusion that the therapeutic efficacy of urethane is of low order and difficult to distinguish from placebo administration.

The present study provides a source of information on the variations over a period of time in patients with multiple myeloma treated with a placebo. Since the equivalent of 100 Gm. of drug as placebo took at least 26 days to administer, and 400 Gm. at least 101 days, the data of tables 3, 5 and 6 can be interpreted to reflect the relative constancy of the parameters listed. They are similar to changes in another group treated with placebo.

In patients similar to those of the present study, this group was able to detect the unequivocal therapeutic activity of phenylalanine nitrogen mustard, a result which tends to validate the methodology used.

**SUMMARY**

Patients with multiple myeloma were stratified according to prior treatment and randomly assigned to coded urethane or placebo syrup administration. Urethane administration was of shorter duration than placebo treatment, but was associated, in patients who received 100 Gm. or more, with leukopenia in the last half of treatment courses. All recognizable beneficial effects were extracted from individual case histories and were found to be nearly equally distributed between the two treatments. Interpretation of the causes of clinical benefit was difficult but there was close temporal relationship to radiation, antibiotics for infection, or corticosteroid administration. Some clinical features and laboratory data of 36 patients with placebo-treated multiple myeloma are provided.

Urethane-treated patients died somewhat earlier on the average than those
treated with placebo. This was ascribable in large part to accelerated mortality in urethane-treated patients who were azotemic.

When hemoglobin concentration, marrow plasma cell content, performance status and azotemia were used to construct a relative ranking prognostic index, among the two-thirds of patients with the worst indexes significantly shorter survival was associated with urethane treatment ($p < .05$). In the best prognostic class, no difference was observed in the survival of urethane- or placebo-treated patients.

Since urethane administration was in no way superior to placebo administration, and was characterized by shortened survival, its use in the doses and schedule employed in this study would appear ill advised.

**SUMMARIO IN INTERLINGUA**

Patientes con myeloma multiple esseva stratificate secundo le modalitate de lor previe tractamento e allocate aleatorimente a gruppss incifrate recipiente urethano e sirop de placebo como agentes medicatori. Le duration del administration de urethano esseva associate in patientes recipiente 100 g o plus con leucopenia durante le secunde medietate del curso therapeutic. Omne le identificabile effectos benefic esseva extrahite ab le diverse historias clinic. Il esseva trovate que lor incidentia esseva quasi identic in le duo gruppss. Le interpretation del causas del beneficios clinic esseva difficile sed un stricte relation temporal esseva notate con irradiation, le uso de antibioticos contra infectiones, o le administration de corticosteroides. Es presentate certe caracteristicas clinic e certe laboratorial pro 36 patientes con myeloma multiple tractate con placebos.

Le patientes tractate con urethano moriva alique plus precocemente que illes tractate con placebo. Isto esseva attribuibile in grande mesura al accelerate mortalitate de patientes a tractamento con urethano qui esseva azotemic.

Quando le concentration de hemoglobina, le contetto plasmocytic del medulla, le stato de performance, e le grado de azotemia esseva usate in le construction de un indice prognostic a scalation relative, le duo tertios del patientes con le indices le minus favorable revelava un association significative ($p < .05$) inter un reducite longevitate e le tractamento a urethano. In le grupp de patientes con le indice prognostic le plus favorabile, nulle differentia esseva observate in le superviventia inter patientes tractate con urethano e illes tractate con placebo.

Viste que le administration de urethano se trovava in nulle maniera superior al administration de placebo e que illo esseva characterisate per un reducite longevitate, le uso de urethano in le doses e le plano therapeutic usate in le presente studio non pare esser recommendabile.

**ACKNOWLEDGMENTS**

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A Controlled Trial of Urethane Treatment in Multiple Myeloma

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