The Clinical Use of Triethylene Melamine

By Sheldon C. Kravitz, M.D.,* Henry D. Diamond, M.D. and Lloyd F. Craver, M.D.

In the spring of 1951, Karnofsky and his associates on the Experimental Chemotherapy Service of the Memorial Center for Cancer and Allied Diseases reported extensively on the use of triethylene melamine (TEM) in treating neoplastic disease.1 This report dealt with the results obtained with this nitrogen mustard-like compound (fig. 1) on 94 patients. From this clinical investigative effort, the pharmacologic actions, toxic effects and dosage schedules for TEM were defined. Following this experience it was decided that the drug should be made available for further investigation by the Medical Neoplasia Service of the Center.

It is the purpose of this paper to report on the results of treatment in 64 patients with neoplastic disorders, mainly those categorized in the malignant lymphoma group.

Methods

Because of the variability in dosage required for each individual and the potential dangers from TEM overdosage, it was decided that the administration of TEM was to be supervised by a single member of the investigative team. In this way therapeutic facility and experience could be obtained with a minimum of risk to the patients.

All patients treated with TEM in the out-patient clinic of the Medical Neoplasia Service received the drug orally. Scored TEM tablets, 5 mg. in size, were used. These were given to the patient only in the number sufficient to cover the prescribed dose before the next clinic visit. All patients were advised to take the TEM with water, upon arising in the morning, at least one hour before breakfast. The patients with Hodgkin’s disease, reticulum cell sarcoma and chronic myelocytic leukemia were usually given successive daily doses of 2.5 or 5 mg. until a total of 10 to 15 mg. was administered. Those patients with lymphosarcoma and chronic lymphocytic leukemia were given similar successive daily doses until 5 to 10 mg. were administered. Most patients were seen at intervals of one to two weeks at the beginning of treatment and never at intervals longer than four to six weeks while being maintained on the drug. No additional TEM was ordered for any patient without knowledge of the white blood cell count and...
hemoglobin level on the day of the clinic visit. After the initial dose of TEM, subsequent doses were ordered depending upon the patient's symptoms and signs of disease, levels of white blood cell count and hemoglobin, and the presence of toxic effects. Succeeding weekly doses were usually in the range of 5 to 10 mg. In some instances of chronic leukemia, weekly doses as high as 15 mg. were found to be necessary. Treatment with TEM was continued until a remission was produced or until bone marrow depression supervened without an associated remission. (A remission is considered to be present when the symptoms and signs

![Chemical Structures: HN2, CH2-CH2CI, CH3-N, CH2-CH2CI](Fig. 1.-Relationship between HN2 and TEM. (Courtesy of Dr. David A. Karnofsky.))

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin's Disease</td>
<td>36</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>8</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>7</td>
</tr>
<tr>
<td>Reticulum cell sarcoma</td>
<td>5</td>
</tr>
<tr>
<td>Bronchiogenic carcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Chronic lymphatic leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>1</td>
</tr>
<tr>
<td>Boeck's sarcoid</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>64</td>
</tr>
</tbody>
</table>

of disease have disappeared completely or have decreased to the extent that the patient is entirely comfortable.) It has been our experience that the average total oral dose necessary to obtain a remission is 35 mg. When a remission is attained, one has the choice of continuing small doses of TEM at intervals of one or two weeks or of discontinuing treatment entirely. TEM was combined with supportive measures such as blood transfusions, antibiotics, analgesics and sedatives when these were indicated. Roentgen therapy was also used in combination with oral TEM when it was felt that this form of treatment would further benefit the patient.

TEM was administered intravenously to the hospitalized patients. Doses of
3 mg. were given on two successive days. This was followed by observation of the patient's clinical and hematologic response for a period of seven to ten days. If, at the end of this time, the patient's symptoms continued and no leukopenia had been produced, another 3 mg. was injected. Nine to 12 mg. given in this manner usually constituted an adequate course of TEM. The intravenous medication was prepared for injection by dissolving 3 mg. of the crystalline material in 10 cc. of sterile physiologic saline. The solution may be given by direct injection with little danger of venous thrombosis, in contrast to the relatively high incidence of this complication from methyl-bis (2-chloroethyl) amine hydrochloride (HN2). These injections were given at various times during the day, unrelated to meals. The concomitant use of such drugs as barbiturates, pyridoxine and dramamine was purposely avoided so that the emetic effect of TEM could be evaluated more precisely.

Table 1 summarizes the types of patients treated and the number of each. All diagnoses but one were proved by biopsy. The single exception was diagnosed as Hodgkin's disease on clinical grounds alone.

### Table 1

<table>
<thead>
<tr>
<th>Hodgkin's Disease</th>
<th>Number of patients treated</th>
<th>Number of patients improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Category II</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Category III</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Category IV</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>32</td>
</tr>
</tbody>
</table>

### Results

**Hodgkin's Disease**

Since patients with Hodgkin's disease vary widely in their complaints and clinical condition, we found it convenient to divide them into four categories in order to evaluate the effects of treatment. Category I consisted of patients who had received no previous therapy. Category II was made up of patients in good general condition with few objective signs of the disease. In Category III were those patients with widespread disease and constitutional symptoms, but still in fairly good condition. Category IV consisted of the latter type of patients who were, however, in poor general condition. Table 2 summarizes the number of patients in each category. It is obvious at once that we did not employ TEM in the early stages of Hodgkin's disease when the manifestations were localized and when no constitutional symptoms were present. We believe that roentgen irradiation is the treatment of choice in these instances.

In Category I both patients had satisfactory remissions from TEM. Both were young individuals. One had her disease two months (from the onset of symptoms) and had enlarged cervical nodes, lung infiltration and fever. Thirty-five mg. of TEM were given orally over a three month period, and this was
followed by roentgen therapy to the lung mass. The patient has displayed no
evidence of active disease for the past sixteen months. The second patient was a
young boy whose symptoms began ten months prior to therapy. He complained
of bone pain and was found to have an osteolytic lesion in the second lumbar
vertebra. Laminctomy and biopsy revealed the presence of Hodgkin's disease.
Postoperatively, generalized adenopathy occurred. The patient was given 6 mg.
of TEM, intravenously, in two doses of 3 mg. each, in two days. This was followed
by roentgen therapy to paraspinal ports as well as to the mediastinum, neck and
groin. Improvement was progressive and the patient was discharged to his home
in another city. Although follow-up was not completely satisfactory, he needed
no further treatment for one year.

Category II consisted of 6 patients whose disease had been present for nine
months to seven years (from onset of symptoms). Four had severe pruritus, 2
had moderately enlarged lymph nodes, 2 had fever and 1 had back pain. All of
these patients were treated with oral TEM, and were still alive, four to sixteen
months after TEM therapy was begun. Only one patient in this group failed to
be improved. This was a Chinese man with pruritus and low back pain without
objective signs of disease. The first course of TEM, 35 mg. in three and a half
weeks, failed to bring about a response. A second course of TEM, 20 mg. again
failed to produce symptomatic relief. It must be stated that neither course of TEM
brought about a leukopenia. The drug was discontinued because the patient
became discouraged with the lack of response. We are usually loath to consider
treatment with TEM a failure unless a leukopenia has been produced. Because
of the individual variation in the oral total dose required, there is no other way
of ascertaining whether a biologic response has been obtained except by evidence
of bone marrow depression.

Two patients in this second category are of extreme interest. One was a young
woman with intractable, generalized itching without demonstrable skin lesions.
All attempts at nonspecific anti-pruritic treatment failed. Twenty mg. of oral
TEM given in nine days (10 mg. initially, then 10 mg. a week later) brought about
a dramatic relief of itching for four months. Then there was a gradual return of
pruritus which was again controlled by 2.5 mg. of TEM every other week. This
patient has been examined in clinic periodically for sixteen months and has no
other evidence of disease. The second case was that of a 29 year old man whose
only evidence of disease for the past two years had been recurrent episodes of
fever. On four occasions he was hospitalized and treated with nitrogen mustard
(HN2) intravenously. On each occasion the patient had a remission for about
six months. When the patient again relapsed he was treated with oral TEM.
Ten mg., given in two days, brought about a prompt fall of the temperature to
normal. This remission lasted for one month. Relapse occurred and 10 mg. of
TEM again brought about a prompt remission, this time for three months. When
relapse occurred at this time, the patient was maintained on TEM, 2.5 to 5 mg.
weekly, with resultant lack of fever for the past eleven months. Although a
moderate anemia appeared, the patient did not develop either a severe leuko-
penia or hemorrhagic manifestations.

Of the remaining 3 patients, one was treated solely for pruritus, 20 mg. of TEM
causing incomplete but sufficient relief from itching to allow discontinuance of
therapy. She went on for fifteen months without further evidence of disease before relapse occurred. A woman with slight lymphadenopathy and pruritus had a remission for six weeks from 20 mg. of TEM given in nineteen days. A man with enlarged nodes and fever had a remission for three months from oral TEM, but relapsed while being maintained on the drug. Continuing the TEM and adding roentgen therapy controlled the relapse.

The 18 patients in Category III had symptoms of Hodgkin's disease for nine months to sixteen years. The average duration of disease from the onset of symptoms to the beginning of TEM therapy was 4.7 years. Five patients received the drug intravenously, the rest took it orally. All patients in this group had some symptomatic or objective benefit from TEM. Remissions varied from one to five months, with most of the remissions lasting two to three months. TEM, given in small doses at regular intervals while the patients were asymptomatic, did not seem to prolong the remissions. Five patients in this category died. Of significance in this group of patients is the fact that, despite the lack of difference from the first two categories in total doses of TEM used, 4 patients developed severe leukopenia and purpura. Three of these patients recovered, while one died with an aplastic anemia. This patient will be discussed in detail under the heading of drug toxicity. Two patients developed severe anemia without marked leukopenia or bleeding. One of these patients responded to transfusions. The other, two months after the cessation of TEM, developed the picture of a hemolytic anemia with jaundice and reticulocytosis. This was followed by leukopenia and thrombocytopenia with subcutaneous and intramuscular bleeding and death.

The differences in response of the various manifestations of Hodgkin's disease are summarized in figure 2. A typical good response to TEM is charted in figure 3.

Category IV consisted of 10 patients, the duration of whose symptoms varied from one to five and a half years. Eight of these patients died. The length of survival after starting TEM ranged from one and a half to fifteen months. The mean survival time was 6.3 months. Despite the apparent ineffectiveness of treatment in this group, it is noteworthy that all but 3 patients were subjectively and objectively improved after TEM. These periods of improvement lasted from...
two weeks to three months. Two patients had second remissions on TEM after relapse. The usual course after relapse, however, was steadily downhill, unaltered by roentgen radiation, cortisone or other chemotherapeutic agents. This group of patients showed greater sensitivity to TEM with respect to bone marrow depression and on the average, smaller doses of TEM had to be used. Two patients in this group exhibited minor bleeding, and their marrow and platelet levels rapidly recovered after the cessation of the drug. As for the symptoms relieved, fever, pruritus, and slightly enlarged lymph nodes responded almost always, whereas bulky nodes, lung infiltration, pleural effusions, and bone disease were affected minimally by the drug.

**Fig. 3.**—Clinical response of a patient with Hodgkin's disease following oral TEM.

**Lymphosarcoma**

Seven patients with lymphosarcoma were treated in this series. Of these, 4 have died and 1 is terminally ill. Two patients received the drug intravenously and 5 orally. Three of the latter group were rapidly approaching the terminal phase of their disease with such signs as general bulky lymphadenopathy, splenomegaly, pleural effusions, bony and skin infiltration and anemia. None of these 3 cases was benefited significantly by the TEM. Two died and one remains critically ill. Of the other 2 who took TEM orally, one was a 65 year old man who had moderately large, generalized lymphadenopathy but was essentially asymptomatic. Over a nine month period this man was given 140 mg. of TEM without producing toxic effects. There was no significant change in the size of the lymph nodes. TEM was finally discontinued because of lack of response. It is noteworthy that roentgen therapy given to the neck, axillae and groins also failed to shrink the nodes. The other patient who received oral TEM was a 41 year old woman who had been ill for approximately one and a half years. She
KRAVITZ, DIAMOND AND CRAVER

was treated previously with roentgen rays and ACTH. The latter brought about a four month remission. When relapse occurred in the form of progressing lymphadenopathy and hepatosplenomegaly, she was given oral TEM, 10 mg. over a two week period. Shrinkage of the peripheral nodes and disappearance of subjective symptoms followed, and for two months she was maintained on 2.5 mg. of TEM every other week. When a new chain of cervical nodes then became enlarged, TEM was increased to 2.5 mg. weekly. She has been on this schedule for three months and is in clinical remission. A total of 82.5 mg. has been given over a period of seven months. Her white blood cell count has ranged between 3,500 and 8,000 per cu. mm. There has been no significant anemia or thrombocytopenia. Minimal anorexia has followed only a few of the doses.

The 2 patients who received the TEM intravenously died. One was an elderly woman with lymphosarcoma of five years' duration. She had periaortic lymphadenopathy, splenomegal}, painful bony infiltration and weakness. She was given 3 mg. of TEM intravenously on two successive days. This was followed by relief of pain, increase in strength and regression of the periaortic nodes. Her white blood cell count was diminished from 5,300 per cu. mm. to 300 per cu. mm. and never recovered to normal levels. Anemia and thrombocytopenia were also produced. After two to three weeks of symptomatic improvement, the patient relapsed rapidly with fever, abdominal pain and epistaxes. She became comatose, without localizing signs of cerebral hemorrhage and only slight increase in the blood urea nitrogen, and died thirty-six days after her first injection of TEM. Autopsy permission was not obtained.

The second patient demonstrated another toxic effect that may be seen with TEM, one which we have reported. This was a 13 year old boy who had been ill with lymphosarcoma for one and a half months. Roentgen therapy given at the onset of the disease resulted in good regression of the enlarged lymph nodes, but rapid relapse occurred. Because of fever and bilateral pleural effusions, despite recent mediastinal roentgen therapy, 3 mg. of TEM were given intravenously twice, with a day of respite in between. Moderate nausea and vomiting resulted. The urine output became markedly depressed and his blood urea nitrogen rose from normal pretreatment levels to 211 mg. per cent, serum potassium rose to 7.2 milli-equivalents per liter and serum uric acid to 32.5 mg. per cent. The carbon dioxide combining power fell to 25 volumes per cent. The white blood cell count fell from 7,000 to 3,500 per cu. mm. The pleural effusions disappeared. On supportive treatment the blood chemical values returned toward normal and there was an increase in urine output. However, the patient did not attain a true clinical remission and after remaining unchanged for one month after TEM, his white blood cell count rose precipitously from normal levels to 200,000 per cu. mm. in five days. His differential smear then showed 80 per cent mature lymphocytes, 13 per cent immature lymphocytes, 4 per cent stem cells and only 3 per cent granulocytes. He became progressively anemic and died after a three month illness which started as lymphosarcoma and terminated with the picture of acute lymphocytic leukemia. The temporary renal failure following TEM administration was believed to be due to the increased endogenous production of uric acid secondary to rapid tissue dissolution.
Reticulum Cell Sarcoma

Five patients with reticulum cell sarcoma received TEM at some time during the course of their disease. All of these patients died of their disease. The survival of these patients from the time of the onset of symptoms was 21 months, 8 months, 15 months, 4 years and 10 months, respectively. The duration of survival from the time of TEM administration was 4 weeks, 4 weeks, 3 weeks, 4 months and 2 months, respectively. It is apparent that TEM was administered in the terminal phases of all 5 cases and that the drug did little to alter the natural evolution of the disease. Each patient had generalized lymphadenopathy and implication of several systems, including hepatosplenomegaly, infiltration of bones and pleural effusions. All the patients had received previous treatment with roentgen rays and 1 patient had previously received a course of HN2. Three patients received their TEM via the intravenous route. The dose varied from 9 to 12 mg. In none of these cases was a severe leukopenia or bleeding produced. One of the 2 patients who received the TEM orally developed a leukopenia of 830 cells per cu. mm. with a subsequent rise to 2,500 cells per cu. mm. No bleeding was noted. In 2 patients, transient, minimal decrease in size of lymph nodes was observed. Two patients with fever had a fall in temperature and 1 had a diminution in bone pain after TEM.

Chronic Myelocytic Leukemia

Eight patients with this disease were treated with TEM and 4 died. All but 1 of the 8 patients received the drug orally. All the patients had active and progressive leukemia despite past treatment with roentgen rays, radioactive phosphorus, urethane and Fowler’s solution. The average duration of disease prior to TEM therapy was 3.4 years (range 1 to 7 years). Two of the 8 patients were terminally ill when they were treated with TEM. Although in both instances the white blood cell count fell and in one the spleen diminished in size, neither patient was symptomatically relieved. Both of these patients died. Of the other 2 patients who died, both had good responses initially to TEM. One of these was in relapse despite urethane and roentgen therapy delivered to the spleen. The other had received considerable splenic irradiation without benefit and his marrow indicated early transition to the acute phase. Coincident with administration of TEM, the marrow in the latter instance actually improved, with disappearance of the myeloblasts and immature myelocytes. These two patients received 105 and 110 mg. of TEM respectively, being treated with weekly doses of 5 to 15 mg. Both patients relapsed while taking TEM and died despite additional therapeutic measures.

Of the 4 patients who are still living, all have made excellent responses, in that they have had symptomatic improvement and lowering of the white blood cell count and 2 have had a decrease in the size of the spleen. (See fig. 4 for one such response.) One patient was of more than routine interest. This man, 43 years of age, had symptoms of his disease for a year and a half before he was seen at the Memorial Center. He was treated initially with roentgen rays to the spleen for splenomegaly, leukocytosis and fever. Treatment brought about an excellent remission, and it was decided to perform a splenectomy at that time. This was carried out uneventfully and the patient was discharged from the hospital with
a white blood cell count of 15,000 per cu. mm. and hemoglobin of 11.5 Gm. per cent. When examined in the out-patient clinic two weeks later, his white blood cell count had risen to 35,000 per cu. mm., and his liver had become enlarged and painful. TEM administration was begun at this time, and the patient received a total of 230 mg. of TEM over a period of seven months, with weekly doses ranging from 5 to 15 mg. There was no further increase in the size of the liver, no lymph nodes became palpable and the hemoglobin fluctuated between 10.5 and 14.3 Gm. per cent. There was no further need for blood transfusions. His white blood cell count for the first four months of treatment never rose above 25,000 per cu. mm. Over the last three months there was a progressive rise in the white blood cell count to a high of 80,000 per cu. mm. without a fall in hemoglobin or platelets—this despite 15 mg. of TEM weekly. The patient, however, remained completely asymptomatic for seven months.

In summary, of 8 patients with chronic myelocytic leukemia, 6 who were not terminally ill, responded favorably to TEM administered in 10 to 15 mg. doses in the first week and 5 to 15 mg. weekly thereafter as maintenance.

**Chronic Lymphocytic Leukemia**

Only one patient with chronic lymphocytic leukemia was treated by us with TEM. (One reason for the relatively small number of cases of lymphosarcoma and lymphocytic leukemia in this series is that ACTH and cortisone were receiving extensive trials in these diseases at about the same time.)

This single patient is of considerable interest since he was treated continuously for one year (fig. 5). When he came to us he was found to have a white blood cell count of 390,000, hemoglobin 9.0 Gm., red blood cell count 3.1 million and platelet count 40,000. He had small but generalized symmetrical lymphade-
CLINICAL USE OF TRIETHYLENE MELAMINE

738

topathy and marked hepatosplenomegaly. No treatment had been given prior to his visit to our clinic. Over the period of one year the patient received 285 mg. of TEM orally without any drop in hemoglobin or evidence of bleeding. At this point the patient's white blood cell count seemed to be fixed at 100,000. It was not until the dose of TEM was increased to 15 mg. weekly that the white blood cell count finally fell to 35,000. This was six months after treatment had begun and after a total of 200 mg. had been given. Despite the fall in the white blood cell count and some shrinkage of lymph nodes, there was very little decrease in the size of the large spleen. During this first six months of treatment, no blood transfusions were necessary, as the hemoglobin was maintained at approximately 10 Gm. per 100 cc., and the patient was asymptomatic. When the white blood cell count fell to 35,000 the weekly dose of TEM was decreased to

![Graph](https://example.com/graph.png)

**Fig. 5.—Treatment of a case of chronic lymphatic leukemia for almost one year with TEM.**

5 mg. Four months later, after satisfactory control on this dose, the white blood cell count rose to 100,000 and the hemoglobin fell to 8 Gm. An increase in TEM reduced the white blood cell count to 15,000 but the anemia and thrombocytopenia became worse. TEM was then withheld and transfusions were given to correct the anemia. The course of this patient is of interest because it has been our general experience that the marrow of patients with lymphosarcoma and lymphocytic leukemia is easily depressed with any of the nitrogen mustards and TEM, yet he was receiving as much as 15 mg. of TEM a week without serious bone marrow depression.

**Miscellaneous**

One patient with Boeck's sarcoïd was treated with oral TEM, 25 mg. in 40 days. This failed to decrease the size of subcutaneous nodules, diminish the cough, affect the roentgenographic appearance of pulmonary parenchymal infiltration, or produce a leukopenia. The patient was subsequently lost to follow-up and all that can be concluded is that 25 mg. failed to do anything to this man's disease.
One patient with extensive mycosis fungoides was treated with oral TEM. Her disease was manifested by generalized skin involvement with severe pruritus, generalized lymphadenopathy and leukocytosis. Ninety-five mg. were given over two and a half months with some depression of the white blood cell count but no observable or measurable effect on the skin lesions, the pruritus, or the lymphadenopathy.

Five patients with far advanced bronchogenic carcinoma were treated with TEM. All but one received the drug intravenously. Three of the patients were in the terminal phase of their disease and TEM did nothing to change this course. All of these patients died. The other 2 patients received three and four intravenous injections of TEM, 3 mg. each, respectively. The TEM was given in conjunction with roentgen therapy. Hence, no conclusions can be drawn in these 2 cases about the efficacy of TEM in primary cancer of the lung. Both patients were somewhat improved following their treatment and are living two years after the onset of their symptoms and seven months after the administration of TEM.

Discussion

It is apparent from the above that we found our greatest use for TEM in the treatment of Hodgkin's disease. When comparing our results with those obtained by Karnofsky in a similar group of patients treated with TEM, we find them to be almost identical. Karnofsky's patients were divided into similar categories and comparisons are easily drawn. The group which differed most was Category I, those patients who had been previously untreated. Our 2 patients had excellent results, whereas one of Karnofsky's patients died from severe bone marrow depression and the other had a poor response plus marked depression of the bone marrow. In the other three categories however, both series indicate that good responses may be obtained initially in almost all cases and that such improvement will last from one to six months, usually approximately three months. When relapse occurs, treatment may again be given with TEM or with any other agent effective in palliating the patient with Hodgkin's disease. Repeated remissions are thus obtainable. When, however, relapse occurs while the patient is being treated with TEM and a leukopenia has been produced, it has been our experience that change of therapy rarely, if ever, brings about significant improvement.

The results that may be obtained with TEM in a patient with Hodgkin's disease depend on the amount of active disease present, its aggressiveness, the presence of constitutional symptoms and the general condition of the patient. We have found that the patient who has slight lymphadenopathy, and fever, sweats and pruritus usually responds well, initially, to TEM. Efforts to maintain remissions in such patients with small, periodic doses of TEM may occasionally be rewarded by a prolonged symptom-free interval. When patients have bulky nodes, lung and bone infiltration or marked hepatosplenomegaly, the response to TEM may be less complete or nil. It is impressive, however, to note the partial response made by many patients with far-advanced disease when TEM is administered. These patients are grateful for the few days or weeks of decreased fever, sweats and itching and diminution of bone pain. In some instances these
responses last a good deal longer than one would have predicted, suggesting that HN2 or TEM should be used at some time during the course of every patient with active Hodgkin's disease.

In the chronic leukemias, TEM appears to be an effective palliative agent. We do not believe that this drug should be used in the early stages of myelocytic leukemia as it is well known that roentgen therapy or radioactive phosphorus, given in a single course, may bring about a remission which will last a year or more. It is at the time when roentgen irradiation appears to be no longer effective or when there is a high white blood cell count with minimal enlargement of lymph nodes and spleen that TEM may be useful. Several of the cases reported here showed good response to TEM after having relapsed on urethane and Fowler's solution. When TEM therapy is discontinued in a patient with chronic leukemia, relapse, or at least elevation of the white blood cell count, usually occurs promptly. It is therefore necessary to find a maintenance dose for each patient and continue this until relapse occurs or toxicity appears.

The indications for treatment of the lymphomas with nitrogen mustard and the results obtained have been recorded in the literature in many excellent articles over the recent years. It would seem that the therapeutic results from treatment with HN2 and TEM are parallel. There are notable differences, however, between the two drugs which make TEM a most useful adjunct in the palliative treatment of the malignant lymphomas and leukemias. The main advantage of TEM lies in its efficacy when given orally. This permits treatment of a large number of patients on an ambulatory basis. The second advantage of TEM, as stated by Paterson, is that it is a "pleasant alternative to HN2 because of less gastric effects." Dameshek reported a 93 per cent incidence of nausea and vomiting after HN2 administration. It is our experience that the incidence of nausea and vomiting after TEM administration, either orally or intravenously, is somewhat less than 50 per cent. In no instance was the nausea or vomiting sufficient to necessitate discontinuance of the drug.

The serious toxicity of TEM consists primarily of bone marrow depression with its sequellae and much less frequently, but nevertheless important, the production of hyperuricemia followed by uremia. The latter complication can be successfully treated if recognized. It is therefore necessary that one be aware of this complication when a patient develops flank pain, dysuria, hematuria, oliguria, fever, drowsiness or other symptoms of uremia after receiving TEM. Proper regulation of fluids, alkalinization of the urine and the establishment of free ureteral drainage by catheterization usually clears up the obstruction to normal renal function.

Depression of bone marrow function may be part of the natural course of any of the malignant lymphomas and leukemias. Leukopenia, per se, is not a contraindication to the use of TEM. In the less advanced cases of lymphoma or leukemia, the bone marrow depression produced by TEM is usually reversible on mere cessation of therapy. In patients with more advanced disease, such depression may be prolonged and even irreversible. Figure 6 charts the course of a patient with progressive and far-advanced Hodgkin's disease who developed an aplastic anemia following the oral administration of only 15 mg. of TEM.
over an eight day period. The aplasia was complicated by retinal hemorrhages. This patient's marrow remained aplastic until her death. In order to avoid such a complication, careful examination of the patient for signs of his disease, for evidence of bleeding in the skin, mucous membranes and ocular fundi, as well as knowledge of the peripheral blood counts are absolute necessities before TEM is given to the patient. In some instances, severe marrow depression will occur despite these precautions. Treatment then consists solely of support. Blood transfusions and antibiotics are most helpful. Cortisone and ACTH have been tried for their stimulative effects on hematopoiesis without much success. Citrovorum factor has been tried in an effort to neutralize the toxicity of TEM, but little benefit has been observed. Toluidine blue, rutin and vitamins C and K

have been tried to stem the bleeding associated with thrombocytopenia and are usually of very little aid.

TEM will soon be more generally available for clinical use, hence a plea for caution would seem to be in order. It cannot be too strongly emphasized that this drug is not the agent of choice in the initial treatment of the usual patient with "malignant lymphoma." Patients with Hodgkin's disease or lymphosarcoma, whose disease is confined to one locus or one region of the body are best treated with local roentgen irradiation. Thorough local treatment of early cases will result in many instances in lengthy remissions and survivals. When palliative treatment of generalized disease is desired, we feel that TEM may be used interchangeably with HN2 without appreciable differences in therapeutic results. For the chronic leukemias, TEM may be added to the armamentarium of agents which include urethane, Fowler's solution, radioactive phosphorus and other general cell poisons.
CLINICAL USE OF TRIETHYLENE MELAMINE

Summary

Triethylene melamine (TEM), a nitrogen mustard-like compound, which can be administered orally and intravenously, has been found to be of considerable clinical use in the palliative treatment of the lymphomas and leukemias. This drug is indicated when a patient presents generalized disease and constitutional symptoms such as fever and pruritus. The incidence of nausea and vomiting following TEM administration is significantly less than that following HN2. The other toxic effects of the two agents are comparable. TEM may be used in conjunction with roentgen therapy. Patients may be maintained on small oral doses of TEM for long periods of time, but extreme caution must be exercised in the oral use of TEM since its tolerance varies considerably with each individual.

REFERENCES

The Clinical Use of Triethylene Melamine

SHELDON C. KRAVITZ, HENRY D. DIAMOND and LLOYD F. CRAVER