Triethylene Melamine in the Treatment of Neoplastic Disease

By R. Wayne Rundles, Ph.D. M.D. and W. Bruce Barton, M.D.*

TRIETHYLENE MELAMINE was discovered to have nitrogen mustard-like effects on experimental tumors and leukemia in mice late in 1949.1, 2 Clinical studies were soon undertaken. In the first series of patients treated with the chemical, Rhoads, Karnofsky and collaborators3 found that temporary periods of improvement comparable to those obtained by injections of nitrogen mustard could be produced in patients with Hodgkin's disease, lymphosarcoma, chronic lymphatic and myelogenous leukemia, and in mycosis fungoides. While no new principle of tumor chemotherapy was involved, the discovery of the new compound seemed to represent a significant advance in practical management. Triethylene melamine, an inexpensive chemical, was found to be effective when given by mouth and did not produce the severe nausea and vomiting or the venous thromboses that sometimes complicate nitrogen mustard therapy. The need for repeated hospital admissions was reduced, and optimally spaced and sustained therapy rendered more feasible. Since a wide use of the new chemical may be anticipated, it is necessary to investigate its safety as a therapeutic agent, and to study its potentialities for prolonged as well as for immediate use, in comparison with and in conjunction with other agents of established value.

The effect of triethylene melamine on normal and neoplastic tissues appears to be identical to that of the nitrogen mustard compounds.3 The action of the latter can be reviewed briefly. The ethylenimonium transformation products of the nitrogen mustards, which form as they are dissolved in body fluids, react with the functional groups of many cell proteins and enzyme systems, inhibit mitoses, produce cytologic alterations, distort cell function and may produce cell death. The tissues predominantly affected are those in which there is active cellular proliferation, particularly the lymphoid tissues and the bone marrow.

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* American Cancer Society Fellow.
The neoplasms especially benefited by nitrogen mustard therapy are those which arise from these tissues also.\textsuperscript{4−12}

Nitrogen mustard and ionizing irradiation are thought to produce similar patterns of tissue injury and delayed cell death.\textsuperscript{5, 13} In the therapeutic use of the two agents anatomic considerations are of primary importance. Roentgen irradiation can be used with the greatest efficiency when the disease is anatomically well circumscribed. Nitrogen mustard therapy affects tissues in widespread anatomic sites on a chemical or functional basis. The effect of the two agents differs in two important respects. Nitrogen mustard appears to act more quickly than roentgen irradiation and the results are shorter lived. Injections must be repeated more frequently for sustained benefit. Bone marrow depression, which is often the limiting factor in the therapy of widespread neoplastic disease, subsides more quickly after the administration of nitrogen mustard and there is usually no cumulative injury after repeated courses of judicious therapy.\textsuperscript{6}

In considering the clinical usefulness of the nitrogen mustards the conditions under which the chemotherapy has been given must be kept in mind. Treatment has usually consisted of a series of 4 to 6 intravenous injections, 0.1 mg./Kg. each, given in a period of a few days. Few patients have been treated except during periods of manifest disease activity, and often not until they had become unresponsive to persistent roentgen therapy. Nitrogen mustard, nevertheless, has been accepted during the last five years as a definite adjunct to irradiation therapy in the treatment of the malignant lymphomas and leukemias.\textsuperscript{5, 6−12, 14, 15} It is regarded as especially valuable in Hodgkin’s disease which has become refractory to irradiation therapy, and in patients with widespread disease with constitutional symptoms. It is perhaps the treatment of choice in those with spinal cord compression, bronchial obstruction, or lesions in the pulmonary parenchyma.

Among the theoretical concepts that influence present day treatment of neoplastic disease of the hemopoietic tissues is the thesis that neoplastic cells are scarcely more sensitive to the destructive effects of irradiation, or to nitrogen mustard compounds, than are the normal cells of their respective tissues of origin.\textsuperscript{3, 6, 14} Block and Jacobson\textsuperscript{17} have recently summarized widely accepted opinions that guide practical therapeutic management. These have evolved out of long experience with agents having little or no curative value, and only limited palliative potentiality, but capable of inflicting much harm. In their opinion the life span of an individual with one of these diseases is not prolonged by treatment, and cure is not to be expected. If the disorder is discovered during an asymptomatic stage, they believe that therapy should not be instituted until symptoms of disease activity develop. Efforts are then directed toward relieving the symptoms rather than in attempting to retard or arrest the course of the disease at an earlier and possibly more favorable stage. Block and Jacobson warn that “any attempt to ‘burn’ the disease out of the patient is not only doomed to failure on theoretical as well as practical grounds, but will invoke a series of complications that are more distressing than the disease itself.” We may expect that as new therapeutic agents are developed, our theoretical concepts may become modified and the results expected from therapy viewed more optimistically.
R. WAYNE RUNDLES AND W. BRUCE BARTON

The present report concerns 134 patients with malignant lymphomas, leukemia and other neoplastic diseases treated with orally administered triethylene melamine (TEM) during a period of 18 months (table 1). The immediate results of therapy are presented and discussed with particular reference to the long-term management of these disorders.

**Table 1.—** *Therapeutic Effect of Orally Administered Triethylene Melamine*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Excellent</th>
<th>Good</th>
<th>Slight</th>
<th>None</th>
<th>Inconclusive</th>
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<td>4</td>
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<td>3</td>
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<tr>
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<td>1</td>
<td>1</td>
<td>2</td>
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<td>7</td>
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<tr>
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<td>1</td>
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<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Reticulum cell sarcoma</td>
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<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
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<td>6</td>
<td>5</td>
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<td>7</td>
<td>3</td>
<td>2</td>
<td>16</td>
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</tr>
<tr>
<td>Leukemia, acute lymphocytic</td>
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<td>2</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>4</td>
<td>2</td>
<td>6</td>
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</tr>
<tr>
<td>Leukemia, myelogenous with pancytosis</td>
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<td>3</td>
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<td>1</td>
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</tr>
<tr>
<td>Leukemia acute myelogenous</td>
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<td>6</td>
<td>7</td>
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</tr>
<tr>
<td>Polycythemia rubra vera</td>
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<td>2</td>
<td>1</td>
<td>3</td>
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<td>3</td>
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<td>1</td>
<td>3</td>
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<td>Adenocarcinoma, oral cavity, with metastases</td>
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<td>1</td>
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<td>1</td>
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</tr>
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<td></td>
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<tr>
<td>Hand-Schuller-Christian disease</td>
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<td>1</td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>134</strong></td>
<td></td>
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</tr>
</tbody>
</table>

**Hodgkin's Disease**

Triethylene melamine was regarded as a suitable agent for trial therapy in patients with disseminated Hodgkin's disease producing generalized symptoms, in those prone to develop new lesions frequently, and in those with disease in anatomic sites, such as the liver and bone marrow, in whom roentgen therapy is ordinarily not productive of good results. Twenty-five patients were treated. The effect of the chemical on the different manifestations of the disease, fever, weakness, lymph node enlargement, pruritis, anemia, etc., was rated as excellent in 9, good in 5, slight in 4, and inconclusive in 7 (table 1). The persistence of
local lesions after otherwise adequate response to TEM over a period of weeks or months was regarded as an indication for supplementary roentgen therapy. In studying the reasons for the variable effect of the chemical in individual patients, it appeared that good or excellent responses occurred characteristically in those who had had no previous treatment or who had developed fresh lesions after earlier roentgen therapy. In those in whom the response was slight or inconclusive the disease was very extensive anatomically, or had been present for a long time and subjected to prolonged therapy with other agents.

The effect of TEM on some of the common manifestations of Hodgkin's disease, its employment in different clinical situations and its effect on a rare complication, Hodgkin's disease with symptomatic or acquired hemolytic anemia, are illustrated by the following 3 cases.

A. F., C99781. This 14 year old colored school boy was first seen at Duke Hospital on October 25, 1950, complaining of a tumor on the side of his neck. Two years previously a small nodule had appeared in the left mid-cervical region and a mass gradually developed in the area. He regarded his general health as good, but his weight during this period fell from a maximum of 101 lbs. to 90 lbs. He had had no weakness, pruritis, chills or fever. On physical examination the only abnormal finding was a lobular, slightly tender mass under the angle of the left mandible measuring 12 x 13 cm. (fig. 1). Lymph nodes in other superficial areas were not enlarged. The spleen was not palpable.

The hemoglobin was 10.7 Gm. per 100 cc., WBC 11,250, RBC 4,600,000, hematocrit 37.8 per cent, and differential white blood count normal. An x-ray film of the chest showed a rounded prominence above the left hilum. A biopsy of the cervical mass showed the typical histologic features of Hodgkin's disease.

He was given 5 mg. of TEM daily for 3 days without side reactions, and then 5 mg. a week for 3 weeks. The tumor became considerably smaller (fig. 1). Because the disease appeared to be predominantly localized and adequate hematologic supervision was difficult, x-ray therapy to the cervical region was then advised. One year after his first visit he had gained 25 lbs. in weight and showed no evidence of disease.
K. S., D2314. This 59 year old widow, admitted to Duke Hospital on November 29, 1950, had become ill with periodic weakness, cough and fever two years previously. A few months after the onset of symptoms, lymph nodes appeared along the left side of her neck and in the right axilla. During the ten months before admission she had had intermittent fever with chills, a severe nonproductive cough and pronounced weakness. Her weight fell from an average of 210 lbs. to 159 lbs.

Physical examination showed a pale, febrile, chronically ill woman with a harassing cough. Numerous cervical and axillary lymph nodes measured 2 to 3 cm. in length, and a large node in the margin of the right pectoralis major muscle measured 3.5 x 4 cm. The tip of the spleen was palpable.

The hemoglobin concentration was 10.2 Gm. per 100 cc., HbC 4,250,000, WBC 17,300, hematocrit 36.0 per cent, reticulocytes 1.5 per cent and platelets 600,000. The differential white cell count was segmented neutrophils 58 per cent, nonsegmented neutrophils 26 per cent, eosinophils 11 per cent, lymphocytes 11 per cent and monocytes 4 per cent. A roentgenogram of the chest showed pronounced widening of the upper mediastinum and areas of infiltration in the pulmonary parenchyma (fig. 2). Bronchoscopy showed no tracheobronchial abnormalities. A cervical lymph node was excised and the pathologic interpretation was Hodgkin's disease.

She was given 17.5 nig. of TEM in 4 days without adverse reaction. The cough subsided. the lymph nodes became smaller and the temperature normal. The leukocytosis persisted for several days and two additional 5 mg. doses of TEM were given.

At home she took 5 mg. of TEM a week for 5 weeks. Her health improved progressively, whereupon she decided to suspend therapy. Ten weeks later weakness, cough, mild chills and fever returned and gradually became worse.

She was re-admitted to the hospital on May 3, 1951. On physical examination she was again febrile but not acutely ill. The superficial lymph nodes were about half their previous size. The spleen was not palpable. Roentgen films of the chest showed less infiltration in the pulmonary parenchyma, but little, if any change in the mediastinum. TEM therapy was re instituted. The fever and leukocytosis promptly subsided (fig. 3).

After returning home the second time she continued taking 5 mg. of TEM each week for nearly 4 months. She became stronger, gained weight and strength and had few complaints. Nine months after the first TEM therapy the superficial lymph nodes were reduced to about one-third their original size. There was further regression in the pulmonary parenchymal infiltration. TEM therapy was then suspended while the residual node enlargements were irradiated.

A. J. M., C90124. This 13 year old colored boy was admitted to Duke Hospital on June 21, 1950, because of poor appetite, listlessness, weight loss, enlarged lymph nodes in the neck and periodic vomiting and fever of 5 months' duration. During his last week at home his family physician thought that he was jaundiced.

On examination he appeared lethargic, undernourished, and chronically ill. The temperature ranged from 37.4 to 38.4 C. There were numerous cervical and supraclavicular lymph nodes 3 to 4 cm. long. His spleen was palpable.

The hemoglobin concentration was 5.5 Gm. per 100 cc., RBC 2,760,000, WBC 5,000, hematocrit 21.0 per cent, MCV 76 cu. µ, reticulocytes 2.3 per cent and platelets normal in
number. The differential white blood count was normal except for a rare immature granulocyte. Bone marrow aspirated from the sternum was of high cellularity. The myeloid-erythroid ratio was 1:1.

Tuberculin and histoplasmin skin tests were negative. The serum proteins were 7.3 Gm. per 100 cc., with albumin 2.4 Gm. and globulin 4.9 Gm. The blood bilirubin was 0.62 mg. per 100 cc.

X-rays of the chest showed widening of the upper mediastinum on the right and an opacity above the right hilum. A cervical lymph node was removed. Sections showed hyalinized fibrous connective tissue and pleomorphic cellular proliferation typical of Hodgkin's disease.

X-ray therapy was given to the cervical lymph nodes and to the mediastinum. His temperature became normal and his strength and appetite improved. After 12 days in the hospital he was able to return home. A re-examination two months after discharge was recommended but he failed to appear.

**Fig. 3.—Hodgkin's disease. Response of temperature and leukocytosis to TEM.**

On November 30, 1950, he was brought back to the hospital critically ill. He had appeared outwardly well until six days previously when signs of an upper respiratory infection and abdominal pain developed. Three days before admission his parents noted yellowish sclerae and dark urine. He rapidly became weak and began to vomit. A few hours before admission he became stuporous.

On physical examination he was thin, acutely ill, deeply jaundiced, and semicomatose. The blood pressure was 90/60, temperature 37.8 °C. Lymph nodes 1 cm. long were palpable in the supraventricular fossae bilaterally. The heart was enlarged and the pulse rapid. The abdomen was tense, but it was thought that the liver and spleen were enlarged.

Blood studies showed a hemoglobin concentration of 2.6 Gm. per 100 cc., WBC 33,300, hematocrit 8.8 per cent, reticulocytes 0.1 per cent and platelets enormously increased in number. The red blood cells could not be counted because of autoagglutination. In the stained blood films the great majority of the leukocytes were neutrophils with an occasional immature granulocyte. Bone marrow aspirated from the sternum was again extremely cellular. The myeloid-erythroid ratio was 1:10.

The urine was dark greenish-brown in color and contained large amounts of urobilinogen and bilirubin. The serum bilirubin was 11.4 mg. per 100 cc. The serum proteins were 8.4
Gm. per 100 cc., of which albumin comprised 2.7 Gm. and globulin 5.7 Gm. The thymol turbidity test was negative.

In preparing for blood transfusion the patient's red cells could not be typed because of pronounced autoagglutination at all temperatures. The antibody could not be removed by washing the cells repeatedly with saline, even up to a temperature of 40 C. (Dr. Ivan W. Brown). His serum agglutinated all available donors' cells in high dilution. He was transfused with Type O, Rh negative packed red cells from 2 pints of blood to which A and B substances had been added. He responded slowly to the transfusions. On the second day a limited exchange transfusion was performed, 2,090 cc. of blood being given and 1,800 cc. removed. Following this procedure a splenectomy was done. He recovered well from the operation and 4 days later was walking about the ward.

His spleen weighed 280 Gm. Sections showed the pleomorphic cellular proliferation characteristic of Hodgkin's disease, acidophilic "paraamyloid" deposit, vascular congestion, pronounced erythrophagocytosis and erythropoiesis. Lymph nodes present in the hilum of the spleen showed similar histologic changes.

Despite the early improvement, intense jaundice and fever up to 38-38.9 C. persisted (fig. 4). On the fourth postoperative day a 2 to 4 p.m. urine specimen contained 20 Ehrlich units of urobilinogen and a barium chloride strip test for bilirubin gave a 2+ reaction in a dilution of 1:10. On the thirteenth day a 2 hour urine specimen contained 67 Ehrlich units of urobilinogen. During the following week he became much worse, developed nausea, vomiting, diarrhea, and required intravenous fluids. The hemoglobin fell to 5.2 Gm. per 100 cc. and he was given a 500 cc. blood transfusion (fig. 4).

Red cells withdrawn soon after his admission to the hospital gave a strongly positive direct Coombs test. Cells removed on the fourth and seventh days gave a negative test, but the reaction was again positive on the ninth and eleventh days.

In view of the evidence of continued hemolysis and known activity of the Hodgkin's disease, 2.5 mg. of TEM were given on the fourteenth and twentieth hospital days, and 5 mg. on the twenty-third day. After the third dose, fever and jaundice disappeared and he began to improve rapidly (fig. 4). On the twenty-eighth hospital day a 2 to 4 p.m. urine specimen contained 6.7 Ehrlich units of urobilinogen. Bilirubin was absent. He was able to return home.
During the next month he felt well and gained 8 Kg. in weight. Re-examination at that time showed that the enlarged lymph nodes had virtually disappeared. The hemoglobin concentration had risen to 10.0 Gm. per 100 cc. The urine contained no bilirubin and the urobilinogen was not elevated. The direct Coombs test was negative and autoagglutination could not be demonstrated even after trypsinization of the patient's red blood cells.

He continued to take 5 mg. of TEM per week at home for 8 weeks. Because adequate hematologic supervision could not be arranged therapy was then suspended. When he returned for a re-examination 4 months after leaving the hospital he had gained another 2 Kg. in weight and had few complaints. Blood counts, however, showed that his hemoglobin had dropped to 5.5 Gm. per 100 cc. The WBC was 1,725, RBC 2,010,000, hematocrit 19 per cent, reticuloocytes 4.1 per cent and platelets 80,000. Bone marrow aspirated from the sternum was found to be almost acellular. Early erythroid and myeloid elements predominated and there were 18 per cent plasma cells. The blood bilirubin was normal. Two months later, without further therapy being given, the hemoglobin had risen to 10.0 Gm. per 100 cc. TEM was then resumed in smaller amounts. Sixteen months after his first hospital admission his general health appeared to be excellent. His hemoglobin remained in the neighborhood of 10.5 Gm. per 100 cc., but there was no sign of active Hodgkin's disease and no evidence of accelerated hemolysis.

In October, 1951, his hemoglobin concentration fell to 8.3 Gm. per 100 cc. The reticuloocytes were 6.1 per cent and the Coombs test was negative. TEM therapy was suspended because of suspected depression of bone marrow function. On December 22, 1951, he was re-admitted to the hospital, again acutely ill. He was icteric and the urine urobilinogen was greatly increased. The hemoglobin concentration was reduced to 2.9 Gm., and reticuloocytes were 53 per cent. The Coombs test was positive. TEM therapy was resumed and there was subsidence of hemolytic activity.

Comment

The etiology of Hodgkin's disease, infectious, neoplastic, or otherwise, remains unsettled, and it is uncertain whether the disease is unicentric or multicentric in origin. In the overwhelming majority of cases the apparent site of origin is in the cervical lymph nodes. In those who die of the disease necropsy studies have shown with great frequency, however, involvement of internal nodes in which disease was not suspected during life.

The long survival of some patients with localized disease who are given surgical or radiologic treatment suggests that Hodgkin's disease may arise unicentrically. The favorable results in this group of patients emphasizes the importance of early diagnosis, and amply justifies aggressive therapy in early cases, although the extent of the node involvement at the outset will often be underestimated.

Patients with localized disease are best treated with irradiation, care being given to deliver adequate dosage to all areas of disease while sparing neighboring tissues, particularly the bone marrow. The frequency with which there are hidden foci, however, may explain the added benefit of whole body irradiation in these instances. TEM, which can be used without producing cumulative tissue injury, may prove to be a more desirable agent for this purpose. Those with disease in many areas may respond well if they are first treated with TEM over a period of weeks or months until maximal improvement has occurred. Residual areas of disease should then be irradiated.

Most authors are of the opinion that the administration of nitrogen mustard in Hodgkin's disease will at best produce only a modest prolongation of life. The following patient, treated with nitrogen mustard injections at intervals...
of 1 to 4 weeks over a period of 6 months, combined with local irradiation, obtained an unusually favorable result which has suggested to us the need for more persistent and aggressive therapy than generally given to those with rapidly recurring and extending disease, and gives some hope in fortunate instances of eradicating tissues exhibiting abnormal proliferative capacities.

C. W. B., B1670. A 37 year old textile worker, was admitted to Duke Hospital on April 23, 1948, for the investigation of a painful tumor that had developed along the right side of his neck in a period of six weeks. He had noted, in addition, weakness and loss of weight. On examination the tumor appeared to consist of a mass of lymph nodes, each about 1 to 3 cm. in length. A questionably enlarged node was palpated in the left axilla. The right tonsil was two and one-half times as large as the left. The remainder of the physical examination showed no abnormalities.

The peripheral blood examination showed no abnormalities except a leukocytosis of 13,300. The bone marrow was normal. X-ray films of the paranasal sinuses, skull, chest and abdomen showed no abnormalities. One of the cervical lymph nodes was removed and the pathologic interpretation was Hodgkin's disease.

Roentgen therapy to a total of 1550 r was given to the enlarged lymph nodes over a period of two weeks. They were soon smaller and in a few days he was able to leave the hospital. One month later, however, a mass developed in the right axilla and the right arm became edematous. X-ray therapy to the axilla was given. The following week he developed abdominal cramps. These became steadily worse until in a few days he had constant pain, abdominal distention and vomiting. He was re-admitted to the hospital. Bulging lymph nodes were present in both axillae. The upper abdomen was distended, peristaltic sounds were increased, and a mass was palpable in the periumbilical area. He was thought to have partial intestinal obstruction. X-ray therapy over the abdomen was started and in a few days the acute abdominal symptoms subsided but he remained generally ill.

Two months after his first visit the lymph nodes in the right axilla had again increased in size, and an exquisitely tender area had developed in the seventh rib on the right. Further roentgen therapy was given with temporary benefit.

On June 14, 1948, he was re-admitted to the hospital, "completely miserable." Enlarged cervical lymph nodes had reappeared. He had pain and stiffness about the right shoulder, edema of the right arm, and abdominal pain with occasional vomiting. An area over the third rib on the right was extremely tender. The consensus at this time was that his condition was hopeless and that with the rapidly advancing and recurring disease he might live for a few months.

In view of the poor prognosis, a plan of giving him nitrogen mustard therapy in the largest tolerated doses at intervals of 10 to 14 days, and continued for as long a period as possible was adopted. The following amounts were given:

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<tr>
<th>Date</th>
<th>Injections</th>
<th>Dose  (mg.)</th>
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<tbody>
<tr>
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<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>8/20</td>
<td>1</td>
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</tr>
<tr>
<td>9/17</td>
<td>1</td>
<td>0.15</td>
</tr>
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<tr>
<td>10/9</td>
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<td>0.15</td>
</tr>
<tr>
<td>11/5</td>
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<td>11/12</td>
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<tr>
<td>11/22</td>
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For 1949:

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<th>Dose  (mg.)</th>
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<td>1/11</td>
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<td>0.3</td>
</tr>
<tr>
<td>1/17</td>
<td>1</td>
<td>0.2</td>
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Total nitrogen mustard 2.0 mg./Kg. (158 mg.)
After the first 4 injections of nitrogen mustard, the lymph nodes became smaller and a moderate fever subsided. The white blood count fell to 2,600 but soon rose to normal. His general condition improved so that he was able to continue therapy as an out-patient. At the end of a month the enlarged lymph nodes had virtually disappeared and he had gained 10 lbs. in weight. He was able to resume work and in spite of later difficulties continued with full-time employment.

Six weeks after beginning the nitrogen mustard therapy he developed a painful tumor about the medial end of the right clavicle. The clavicular tumor became smaller and less painful 2 to 3 days after each injection of nitrogen mustard, but in another 7 to 10 days would recur. By November 22, 1948, the clavicular tumor had grown to measure 8 x 8 cm. A few days later the overlying skin ulcerated, and bony fragments were discharged. An abdominal mass again became palpable. Between November 27 and December 6, 1948, irradiation to a total dose of 1,000 r was given over the clavicular tumor and to the abdominal mass to a total dose of 900 r. In January, 1949, the ulcerated area overlying the clavicular tumor increased in size and further nitrogen mustard therapy was given. Shortly after this the ulcer healed, and all manifestations of the disease disappeared. He has been seen frequently during the following 3 years. There has been no evidence of disease reactivation at any time.

FOLLICULAR LYMPHOMA, LYMPHOCYTIC AND LYMPHOBLASTIC LYMPHOMA, AND RETICULUM CELL SARCOMA

Twenty patients with malignant lymphomas of the above varieties were selected for trial therapy with triethylene melamine. Like those with Hodgkin's disease, all had widespread lymph node involvement. Abnormal leukocytes were not present in the circulating blood. Bone marrow aspirated in 18 patients was normal. Abnormal lymphoid cells were aspirated from an area of sternal tenderness in one patient, and in one instance the marrow was not examined.

Constitutional symptoms were uncommon during the early phases of the disorder, in contrast with those with Hodgkin's disease, and there was even less tendency for the lymphatic involvement to remain localized. The commonest presenting symptom was the appearance of one or more lymphoid tumors. Splenomegaly preceded the development of enlarged superficial lymph nodes in one patient. In 4 other instances the presenting sign was rectal bleeding due to infiltration of the lower bowel, edema of the legs with proteinuria, severe steatorrhea, and nonthrombocytopenic purpura, respectively.

In some respects the group was heterogeneous. Two 4 year old boys were included. Two of the adults with rapidly progressive disease died within 6 months of the appearance of their first symptom, in contrast to 5 patients who lived for 5 to 8 years while being given periodic irradiation therapy. Half of the group had had no treatment before being given TEM.

The overall therapeutic effect of TEM in this group was judged largely by the reduction in size of local tumors. The results were rated as excellent in 7, good in 3, slight in 5, none in 3 and inconclusive in 2 (table 1). The good to excellent results occurred predominantly in 2 groups: (1) patients with newly developed tumors, some of whom had been previously treated successfully with irradiation, and (2) patients given TEM as their initial therapy. Poor results occurred in those with rapidly extending or recurring disease, and in those with tumors causing severe pain, suggestive of local tissue invasion by the malignancy. In 3 of the patients in whom the drug apparently had little or no effect, gastro-intestinal symptoms and/or leukopenia were not produced. The dose of the chemical, accordingly, might have been inadequate. No clear differentiation in clinical fea-
tures, or in the response to therapy, was discernible between those diagnosed as having lymphocytic lymphoma and those having lymphoblastic lymphoma. Two of the patients with follicular lymphoma who were little benefited were treated late in the course of their disease. One patient diagnosed as having reticulum cell sarcoma 4 years previously, had extensive abdominal disease with ascites at the beginning of TEM therapy and responded slowly over a period of months.

The following patient with lymphocytic lymphoma is illustrative of what was regarded as an excellent therapeutic result.

![Image of patient C. P., C96789.](image)

**Fig. 5.—C. P., C96789. Reduction in size of lymph nodes in malignant lymphoma after TEM therapy.**

*C. P., C96789.* This 50 year old colored preacher and farmer was admitted to Duke Hospital on September 25, 1950, complaining of tumor masses in his neck. A nodule had first appeared under the angle of the mandible on the right three or four years previously. This fluctuated in size for some months, but then began to enlarge steadily. About one year before admission masses began to appear on the left side of his neck, in the axillary, inguinal and epitrochlear areas. For 3 or 4 months he had had cough and dyspnea when lying supine, but he was able to continue with hard manual labor.

On physical examination there was massive lymph node enlargement in all superficial areas (fig. 5). The liver and spleen were palpable. The hemoglobin was reduced to 11.7 Gm. per 100 cc. The WBC was 7,800. No abnormal cells were present in the circulating blood. Marrow aspirated from the sternum was extremely cellular and contained no abnormal leukocytes. An x-ray of the chest showed no mediastinal or pulmonary parenchymal abnormality. Biopsy of a cervical lymph node showed dense lymphocytic infiltration with
obliteration of the node architecture. The pathologic interpretation was lymphocytic lymphoma.

He was given 5 mg. of TEM daily for 4 days. With the fourth dose he developed anorexia and mild nausea that lasted for several hours. Six days after the first TEM was given the WBC had fallen to 3,100, but soon rose again to normal. The lymph nodes at this time were considerably softer and possibly smaller.

On re-examination two months later, the superficial lymph nodes were definitely smaller. He was advised to take two additional 5 mg. doses of TEM. A few weeks later he developed pneumonia, and when given a variety of medications became acutely disturbed and psychotic. He recovered when the administration of drugs was discontinued.

Four months after his first visit he regarded his general health as quite satisfactory. The lymph nodes were about one-fifth their original size (fig. 5). There were no other significant abnormalities. He was advised to continue taking periodic doses of TEM.

Comment

The therapeutic problems presented by patients with follicular, lymphocytic and lymphoblastic lymphoma, and reticulum cell sarcoma vary from those encountered in Hodgkin's disease to those in lymphocytic leukemia. Bulky tumors usually respond well to local roentgen irradiation. The widespread involvement of lymphoid tissue in most cases, however, indicates the advisability of generalized therapy. TEM appears to be a most promising agent for this purpose.

CHRONIC LYMPHOCYTIC LEUKEMIA

(A) Leukemic Group

Twenty-three patients having chronic lymphocytic leukemia with high leukocyte counts were treated with TEM. All patients with this disease were regarded as suitable for trial therapy. The disease was of recent onset in 11 of them and TEM was the first anti-leukemic therapy given. Most of the others had been given x-ray therapy earlier for disease of 18 months to 7 years duration. The therapeutic effect of TEM was judged by the degree to which the primary manifestations of the disease—lymphocytosis, lymph node and splenic enlargement and related symptoms—could be affected without producing or increasing depression of bone marrow function. The results were considered excellent in 12 patients, although in 2 of them pre-existing anemia due to bone marrow replacement was never overcome; good in 6, 2 of whom remained anemic; and slight in 5. In those to whom TEM was of least benefit, the leukemic process was advancing rapidly and the abnormal cells were more immature.

The following 4 case histories illustrate variation in effective TEM dosage, the production of a long remission in a patient treated for asymptomatic disease, hematologic improvement in a patient with leukemic marrow infiltration, and the failure to improve the anemia in 2 patients with leukemic marrow replacement.

D. C. L., B-38020. This 73 year old farmer was admitted to Duke Hospital on August 3, 1950, for the excision of an ulcerating carcinoma of the right cheek. Except for 4 or 5 attacks of transient precordial pain that had occurred on exertion during the previous two or three years, his general health had been good. Physical examination revealed a few superficial lymph nodes 0.5 to 1.0 cm. in length, moderate cardiac enlargement, and the liver and spleen to be palpable 3 to 4 cm. below the respective costal margins. Blood study showed a WBC of 127,000, 93 per cent of which were immature lymphocytes. The hemoglobin was 12.0
Gm. per 100 cc., hematocrit 38.8 per cent, reticulocytes 1.2 per cent and platelets normal in number.

The carcinoma was excised and the defect repaired.

TEM therapy was begun during his convalescence. Five mg. were given daily for 3 days (fig. 6). There were no side reactions. A month later the white blood count had fallen to 47,500. Two additional 5 mg. doses of TEM were prescribed. During the following weeks the WBC fell to a range between 8,000 and 13,000. The enlarged superficial lymph nodes disappeared and the liver and spleen regressed until they were not palpable.

Eight months after his first TEM therapy, he developed a prolonged upper respiratory infection and finally lobar pneumonia, with pneumococci type VII in the sputum. Despite intensive antibiotic therapy, pulmonary cavitation occurred. His convalescence was slow and required 4 weeks in the hospital.

On re-examination 16 months after his first therapy he appeared to have excellent general health. Physical examination showed no significant abnormalities. The only hematologic

![Graph](image-url)

Fig. 6.—Hematologic response to TEM in a patient with asymptomatic lymphocytic leukemia.

abnormality was a small percentage of immature lymphocytes in the circulating blood, despite 8 months without anti-leukemic therapy.

G. W. L., C18920. This 39 year old colored farmer was first seen at Duke Hospital on October 3, 1947, complaining of frequent sore throats and enlarged "neck glands" for 3 years. On physical examination his tonsils were huge. Lymph nodes in the cervical, axillary and inguinal areas measured 1.0 cm. or more in length. The hemoglobin concentration was 15.0 Gm. per 100 cc., RBC 5,130,000, and WBC 17,000, of which 70 per cent were abnormal lymphocytes. Sections of a lymph node removed from the neck showed lymphocytic infiltration and obliteration of the node architecture.

He was given x-ray therapy to the superficial lymph nodes. On re-examination one month later the nodes were considerably smaller and the white blood count was 5,450.

He was not seen again for 3 years when he returned with the same complaints as before. On this occasion the superficial nodes measured up to 3 cm. in length. His spleen was palpable several cm. below the rib margins. The hemoglobin was 11.7 Gm. per 100 cc., RBC
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4,610,000, hematocrit 38.0 per cent and WBC 116,000, of which 92 per cent were abnormal lymphocytes. Reticulocytes and platelets were normal in number. Marrow aspirated from the sternum contained 93 per cent immature lymphocytes and very few myeloid or erythroid cells.

TEM therapy was instituted in doses of 2.5 to 5.0 mg. per day (fig. 7). There were no side reactions. After two months of therapy the nodes were much smaller, the spleen was not palpable, and the WBC ranged from 12,000 to 14,000. The hemoglobin subsequently rose to within range of normal. At 8½ months he considered his general health as entirely satisfactory. Re-examination of the bone marrow showed fewer lymphocytes and an abundance of erythroid and myeloid cells.

J. C. S., C1150. This 60 year old man was first seen on February 21, 1947, and followed closely for nearly 5 years. Six months before his first visit he had become ill with chest pain and fever. A few weeks later enlarged cervical lymph nodes appeared. An x-ray of his chest showed masses in both hila. Biopsy of a cervical node showed heavy lymphocytic infiltration and obliteration of the normal node architecture. He was referred to us for therapy.

Physical examination showed pronounced enlargement of the tonsils. The cervical and inguinal lymph nodes measured 1 to 2 cm. in length. The hemoglobin concentration was 13.5 Gm. per 100 cc., and the WBC was 33,000 of which 82 per cent were abnormal small lymphocytes. He was given x-ray therapy to the enlarged superficial and hilar lymph nodes. The former disappeared but the latter changed very little. The WBC remained moderately elevated. Additional roentgen therapy was given to the hilar areas two months later.

Eighteen months after his initial visit he developed chronic suppuration of the left tear duct. Physical examination showed no other relevant abnormalities. His hemoglobin was 11.5 Gm. per 100 cc. and the WBC 41,000. The predominant cells in marrow aspirated from the sternum were early lymphocytes. Erythroid and myeloid elements were greatly reduced. Whole body roentgen irradiation was administered. During the ensuing months the white blood count dropped to normal levels but his hemoglobin continued to fall.

He was re-admitted to the hospital two years after his first visit because of progressive

Fig. 7.—Hematologic response to TEM in a patient with chronic lymphocytic leukemia with mild anemia and lymphocytic bone marrow infiltration.
anemia. He was given 4 injections of nitrogen mustard intravenously, 0.1 mg./Kg. each during a period of 8 weeks. Three weeks after completing the therapy he became extremely weak and had mild generalized purpura. The WBC was found to be 4,000, the hemoglobin 5.2 Gm. per 100 cc., and the platelet count 60,000. Re-examination of the bone marrow showed it to be virtually acellular. After he was given 3 blood transfusions of 500 cc. each he became more comfortable and had no further bleeding.

During the following 17 months he required 2 to 4 blood transfusions every 4 to 6 weeks to maintain comfortable blood levels. At the end of this time the superficial lymph nodes enlarged again, the spleen became palpable and the WBC rose to 48,000 to 57,000.

TEM therapy was instituted with caution and continued for over a year. With an average dose of 2.5 mg. per week the superficial lymph nodes disappeared, the spleen regressed in size, and the white count was held within range of normal. He did not develop thrombocy-

![Fig. 8.—Persistence of anemia after TEM therapy in patient with chronic lymphocytic leukemia with leukemia marrow replacement of long standing.](image)

...topenia or hemorrhagic manifestations. Blood transfusions, however, continued to be required at regular intervals.

J. W., D17739. This 64 year old colored man was first seen at Duke Hospital on July 9, 1951. He had had gradually enlarging lymph nodes about his neck for some 18 months. For a year he had had weakness, ease of fatigue and dyspnea on exertion, and for 3 to 4 months his legs had been grossly edematous.

On examination large masses of lymph nodes were present in the cervical, axillary and inguinal regions. The liver edge was 10 cm., and the tip of the spleen 3 cm. below the rib margins. Hard, non-pitting edema involved the legs to the groins, and the external genitalia were edematous.

The hemoglobin concentration was 6.8 Gm. per 100 cc., RBC 3,030,000, hematocrit 21.0 per cent and WBC 587,000, 97 per cent of which were abnormal lymphocytes. The platelets were moderately reduced in number. Marrow aspirated from the sternum contained virtually nothing but abnormal lymphocytes.

He was given TEM in 2.5 mg. doses to a total of 22.5 mg. in a period of 2 weeks. The last 3 doses were probably given inadvertently considering the precipitous fall in WBC
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(fig. 8). The hemoglobin and red cell count continued to fall until blood transfusions were required. Satisfactory blood counts were still not maintained 6 months after the beginning of therapy.

Comment

Minot and Isaacs emphasized in 1924 the grave prognostic significance of the development of anemia and, or thrombocytopenia—indications of bone mar-

Fig. 9.—J. D. O., C38338. A 49 year old farmer was found to have chronic lymphocytic leukemia in July, 1948. Enlarged superficial lymph nodes had been present for 6 months. The hemoglobin concentration was 14.0 Gm., RBC 4,300,000, hemocrit 38.0 per cent, and WBC 30,000. The bone marrow was normally cellular but 60 per cent of the cells were lymphocytes. He was given nitrogen mustard injections at intervals of 1 to 3 months for two and one-half years, and during this time enjoyed excellent health. His physical and hematologic status remained, however, substantially unchanged. He was then given TEM for a year, the average dose being 2.5 mg. every two weeks. During this period the lymph nodes became smaller, and WBC was held virtually within range of normal. Lymphocytic infiltration disappeared from the marrow.

A Photograph (X400) of marrow aspirated on March 29, 1950, showing reduced myeloid and erythroid elements, and lymphocytes 65 per cent.

B Photograph (X400) of marrow aspirated on November 23, 1951, showing numerous granulocytes and normoblasts, and lymphocytes 16 per cent.

G. B. T., D6424. This 45 year old physician, had had increasing sensitivity to cold for twelve years, and progressive anemia for five years. The hemoglobin was eventually reduced to 6.4 to 6.8 Gm. per 100 cc. He was found to have hypoa1buminemia and cryoglobulinemia. The bone marrow contained virtually nothing but primitive lymphoid elements.

C Photograph (X400) of marrow before treatment.

He was given TEM for 10 months. The hemoglobin concentration was then 11.2 Gm. per 100 cc. and the bone marrow was virtually normal.

D Photograph (X400) of marrow showing numerous granulocytes and normoblasts.
row involvement—in the course of chronic lymphocytic leukemia. The important causes of disability and ultimate fatality in this disease, infection, anemia and hemorrhage are attributable in large measure to replacement of the bone marrow by infiltrating or proliferating lymphocytes. Large numbers of abnormal lymphocytes were present in the bone marrow in 19 of our 22 patients before TEM therapy was started. No examination was made in one instance. Tissues other than the bone marrow, such as the liver, heart muscle, etc. were less commonly the sites of serious leukemic damage.

A major object in the early treatment of patients with chronic lymphocytic leukemia, even in an asymptomatic stage, should be the prevention of bone marrow invasion and damage. There is little evidence that the irradiation of superficial lymph nodes or of the spleen delays or protects against bone marrow involvement. Whole body irradiation or radioactive phosphorus therapy may be of more value, especially when given in regularly spaced, individually titrated doses. Once marrow replacement has occurred, as evidenced by granulocytopenia, anemia or thrombocytopenia and substantiated by the findings on direct marrow examination, therapy of any type entails greater risk and is often ineffective. All forms of irradiation under these circumstances, as well as nitrogen mustard as commonly used, have failed to improve bone marrow function significantly, or to reduce lymphocytic infiltration.

The extent to which damage to the bone marrow and to other vital tissues can be prevented by sustained TEM therapy in any significant number of patients with chronic lymphocytic leukemia is still to be determined. Our observations thus far are encouraging. In the 2 patients in this series with normal bone marrow before therapy, and in the 10 with marrow infiltration but no anemia, neither persistent anemia nor thrombocytopenia has developed either as a result of therapy or of progression in the disease. In several instances, marrow that was once heavily infiltrated was later found to contain fewer lymphocytes or to be entirely normal (fig. 9).

Two of the 9 patients who had anemia with bone marrow infiltration and replacement at the outset had substantial hematologic improvement following TEM therapy. Four responded poorly to TEM, or died soon after it was started, without showing definite improvement in marrow function. In 3 patients the primary disease responded well to TEM, but anemia due to marrow replacement, which had been present for some months, persisted and continued to require repeated blood transfusions. It appears that bone marrow damage produced by leukemia becomes irreversible in the course of time.

**CHRONIC LYMPHOCYTIC LEUKEMIA**

**(B) Sub-Leukemic Group**

Sixteen patients with chronic sub-leukemic lymphocytic leukemia were treated with TEM. The leukocyte count was normal or low in all cases. Abnormal lymphocytes were constantly present in the circulating blood. The disease appeared to be of less than one year's duration in 10 patients when treatment was begun. Five died within a year of onset of their symptoms. Examination of the bone marrow before treatment showed no abnormality in 3 patients, lymphocytic
infiltration in 1 who was not anemic and lymphocytic replacement in 11 who were anemic.

The response of this group to TEM was generally poor, in contrast to that of the group with chronic lymphocytic leukemia in which the leukocyte count was elevated. The therapeutic effects were excellent in 4, slight in 7, absent in 3 and inconclusive in 2. The less favorable results in this group seemed to be due to the basic severity of the disease, to the high incidence of bone marrow replacement and in some cases to delay in recognition and the initiation of treatment. The following case history illustrates an excellent therapeutic result in a patient whose prognosis would ordinarily be grave.

M. W., C97651. This 30 year old white married woman was first seen on October 1, 1950. Two years previously she had developed nasal obstruction and nodular tumors about her upper eyelids. Orbital tissue was removed for pathologic study at another hospital and a diagnosis of lymphatic leukemia made. The orbital tumors disappeared following x-ray therapy and she became outwardly well.

Two months before her hospital visit she became weak and pale was found to be severely anemic. She was given a total of 1500 to 2000 cc. of blood intravenously on three occasions with symptomatic relief, but the anemia recurred each time in a matter of 2 to 4 weeks.

Physical examination showed obesity, no jaundice, lymph nodes in the left axillary, epitrochlear and inguinal regions measuring up to 1 to 3 cm. in length and moderate splenomegaly.

The hemoglobin concentration was 10.2 Gm. per 100 cc., RBC 4,140,000, WBC 6,500, hematocrit 34.0 per cent and reticulocytes and platelets normal in number. The white cell differential count was neutrophils 23 per cent, nonsegmented neutrophils 10 per cent, metamyelocytes 1 per cent, eosinophils 2 per cent, monocytes 10 per cent and abnormal lymphocytes 55 per cent. Bone marrow aspirated from the sternum was highly cellular. The predominant cells were immature lymphocytes, but small islands of normal marrow tissue persisted. Urine and stool analyses, blood bilirubin concentration and the excretion of bromsulfalein dye were all normal. Serologic tests for syphilis and a direct Coombs test were negative.

She was given 3 doses of TEM, 5 mg. each, in 4 days. The lymph nodes became smaller. She returned home and during the following week anemia severe enough to require 2 blood transfusions recurred.

Twenty days after the first TEM therapy, the superficial lymph nodes had disappeared and the spleen was barely palpable. The hemoglobin was 6.8 Gm. per 100 cc., RBC 2,400,000, WBC 1,800, hematocrit 19.5 per cent and platelets and reticulocytes normal in number. Re-examination of bone marrow showed a great reduction in total cellularity. Only a few lymphoid cells and a few early erythroid and myeloid elements were present in the aspirated bone marrow.

At home she improved rapidly and was soon feeling “wonderful.” She was given about 10 mg. of TEM in small doses during the following 5 months. Re-examination 10 months after her first visit showed no significant physical abnormalities. The hemoglobin concentration was 13.5 Gm. per 100 cc., RBC 4,700,000, WBC 7900, hematocrit 44.0 per cent, reticuloocytes 1 per cent and platelets normal in number. Twelve per cent of the leukocytes in the circulating blood were immature lymphocytes.

Leukemia, Acute Lymphocytic

Three patients with acute lymphocytic leukemia, 21, 3 and 12 years old respectively were treated with TEM. The youngest child, treated with the chemical alone, obtained definite symptomatic benefit for a period of 8 to 10 weeks. Persistent leukopenia and increasing anemia associated with low marrow cellularity then made another type of therapy necessary. The second child, ill for
5 weeks, had severe anemia and thrombocytopenia when first seen. TEM given over a period of 2 months was of no symptomatic or hematologic benefit. The third child had had a malignant lymphoma excised from the scalp at the age of 8 years. Four years later he developed, in a few weeks time, multiple subcutaneous tumors, leukocytosis with large, immature lymphoid cells in the circulating blood. The bone marrow soon became infiltrated and replaced. The disease was rapidly fatal and its course was not altered by TEM therapy.

**Leukemia, Granulocytic**

Six patients with chronic granulocytic leukemia were given TEM therapy. One patient had untreated disease. The other 5 had been given urethane for 10 to 40 months, until incipient liver disease or intolerance to therapeutically adequate doses of the chemical made it necessary to change the plan of therapy. Three of the group responded quickly to TEM. Fever, bone tenderness, splenomegaly and granulocytosis subsided and the anemia began to regress. A fourth patient responded slowly, only after about 100 mg. of TEM had been given over a period of 6 months. The patient with previously untreated disease responded poorly and after 25 days remained ill, although a 50 per cent reduction in white blood count had occurred. She then responded satisfactorily to urethane.

Three patients with chronic granulocytic leukemia with variable degrees of erythroid and megakaryocytic overgrowth (panmyelosis) were treated without definite benefit.

A patient with chronic subleukemic granulocytic leukemia was given sufficient TEM to reduce the WBC for several weeks without altering the course of her disease.

Seven patients with acute granulocytic leukemia were treated with TEM. The chemical was effective in reducing leukocytosis during the period of its administration but noteworthy symptomatic or hematologic benefits were not produced.

**Polycythemia Vera**

Three patients with newly discovered polycythemia vera, all of whom had been subjected to phlebotomy until the erythrocytosis was controlled, were given TEM in an effort to prevent the return of excessive marrow activity. A substantially normal hematologic status was maintained for periods of 7, 12 and 14 months respectively. When therapy was suspended in the patient treated for 7 months relapse occurred within a few weeks.

**Multiple Myeloma**

Three patients with multiple myeloma were treated with TEM after their disease had become refractory to urethane. Depression of bone marrow function was produced in all of them without a definite effect on the growth of plasma cells being observed, although in one instance the amount of abnormal gamma globulin in the serum was slightly reduced.

**Miscellaneous Neoplasms**

Twenty-two patients with widespread tumors not primarily of hemopoietic origin were given TEM therapy (table 1). Worthwhile palliation was observed...
only in those with lymphoepitheliomas arising from the nasopharynx and in those with papillary cystadenocarcinomas of the ovary. The following cases are illustrative.

A. R. S., C94715. A 14 year old white boy, was referred to Duke Hospital on August 21, 1950. He had been well until 21 months previously when a painless mass began to grow on the left side of his neck. A few weeks later a similar mass developed on the opposite side. He was examined by his family physician who found a tumor in the nasopharynx. A portion of the latter was taken for biopsy but the pathologic interpretation was in doubt.

On physical examination firm masses in the posterior cervical areas measured 5 x 7 cm. and 3 x 5 cm. (fig. 10). The nasopharynx was filled with a friable nodular tumor which obstructed the right posterior naris. Study of the peripheral blood and bone marrow disclosed no abnormality. A mento-vertex film of the skull showed irregularity in bone density and areas of destruction. Biopsy specimens were taken from the cervical and nasopharyngeal tumors. The pathologic interpretation was lymphoepithelioma with metastasis.

He was given 22.5 mg. of TEM over a period of 5 days without adverse reaction. One month later there was a conspicuous reduction in the size of the cervical metastases (fig. 10). Two 5 mg. doses of TEM were given during the following month but the masses became slightly larger. Roentgen therapy was then given to the nasopharynx and neck.

Three months after his first visit the mass on the left side of his neck measured 2 x 2 cm. while that on the right side had disappeared. Examination of the nasopharynx showed no abnormality. At home he took 2.5 to 5 mg. of TEM per week, adjusting the dose to maintain a slight leukopenia.

Seven months after his initial visit a tumor appeared in the frontal region. In three weeks it increased in size to measure 2.5 x 3.5 x 4.5 cm. An x-ray of the skull showed destruction of the bone underlying the tumor.

Roentgen therapy was administered to the tumor and TEM was suspended for a month. During this time he developed several enlarged cervical nodes, one of them in the left supraclavicular fossa measuring 3 x 3 cm. TEM was resumed in the largest amounts permitted by the blood counts and during the ensuing weeks all cervical tumors disappeared. Periodic doses of TEM were continued. Re-examination 18 months after he was first seen revealed no evidence of disease.

J. C., D25477. This 14 year old school girl became aware of a mass in the lower abdomen
in May, 1951. She was operated upon and an ovarian tumor was partially resected. The pathologic diagnosis was papillary cystadenocarcinoma. She was given roentgen therapy for over 30 days and for 4 months enjoyed good health. She then developed chronic fatigue, dizzy spells and nausea. Examination disclosed hepatomegaly and a mass in the lower abdomen. Fluoroscopy of the chest showed elevation of the diaphragm on the right side. She became rapidly worse with chest pain and fever, and was admitted to Duke Hospital on October 23, 1951.

Physical examination showed signs of pleural effusion on the right, a greatly enlarged liver and a tender mass in the lower abdomen. The temperature ranged from 38 to 39 C. Hematologic study showed a normocytic, normochronic anemia with the hemoglobin concentration reduced to 9.9 Gm. per 100 cc. Serial roentgen films of the chest showed rapid progression in her disease (fig. 11). Thoracentesis was performed and about 400 cc. of bloody fluid removed.

Between the second and fifth hospital days she was given nitrogen mustard intravenously to a total dose of 0.45 mg./Kg. She improved and therapy was continued with TEM at home. Six weeks after her initial visit she had no complaints and was able to return to school. The abdominal mass was no longer palpable and the liver was normal in size. A roentgenogram of the chest showed considerable improvement (fig. 11). The hemoglobin concentration had risen to 10.8 Gm.

**Fig. 11.**—Serial chest roentgenograms of patient with metastases from an ovarian cystadenocarcinoma, showing increase in disease, and then regression following nitrogen mustard and TEM therapy.

**Discussion and Summary**

The therapeutic effect of triethylene melamine (TEM) on neoplastic disease as reported by Karnofsky and collaborators has been confirmed in 134 patients treated over a period of eighteen months. The discovery of this chemical has permitted significant advances in practical therapy. Its effectiveness when given by the oral route and its relative freedom from disturbing side reactions, in contrast to nitrogen mustard, make optimally spaced and sustained therapy feasible. Its generalized action renders it an agent suitable for the treatment of diseases which involve tissues in widespread anatomic areas.

As summarized above in reference to different disease entities, TEM has proved to be especially useful in the treatment of the chronic proliferative diseases arising from lymphatic tissue. Localized Hodgkin's disease and localized lymphomatous tumors continue to be best treated with roentgen irradiation. Combined local and systemic therapy is probably indicated in the majority of patients. In managing diffuse nonlocalized disease, TEM is a promising agent which may compare favorably with whole body irradiation and P₃₂. When the bone marrow is involved, as in chronic lymphocytic leukemia, the beneficial effect of TEM administration appears to surpass that of any other agent.

Although TEM may suppress the growth of normal bone marrow constituents to a very pronounced degree, its therapeutic effect in the myeloid proliferative
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Diseases has been somewhat disappointing. In atypical and subleukemic granulocytic leukemia and in multiple myeloma the results have not been promising. The long term effect in polycythemia vera merits further study. In the small number of patients with chronic granulocytic leukemia in this series, the results seem to be inferior to those achieved by urethane. To evaluate the comparative merits of different therapeutic agents in this disease will require a large-scale cooperative study.

In acute leukemia, rapidly progressing malignant lymphomas, and in most nonhemopoietic tumors TEM therapy has been of little value. Worthwhile palliation has been observed in nasopharyngeal lymphoepithelioma and in ovarian papillary cystodemocarcinoma with metastases. Additional study of the effect of TEM on these tumors is indicated.

The critical problem in TEM therapy is the administration of therapeutically adequate amounts of the chemical while avoiding the serious hazards of overdosage. The correct dose cannot be forecast but must be determined empirically for each patient. The effective intravenous dose is one-fourth to one-half that of nitrogen mustard, or in adults 2 to 3 mg. daily for 2 to 3 days. Oral doses range from these amounts upward. The effective total dose of TEM during the first 1 to 3 weeks of treatment averages 15 to 25 mg. About 1 patient in 10 will develop temporary depression of bone marrow function when given as little as 8 to 12 mg. of TEM in a span of 5 to 7 days. Few may take 10 to 15 mg. per week almost indefinitely with little result. The reaction of an individual patient to given amounts fortunately remains relatively constant, except that increased sensitivity will occasionally develop after it has been used for some weeks or months.

The considerable variation in effective dose that occurs in different patients does not appear to be related to the type of disease they may have. Greater caution should be exercised, however, in those with pre-existing bone marrow damage. The chemical decomposes when in contact with organic materials, and in an acid medium. Differences in dosage requirements may possibly be due to variations in gastric acidity or to the facility with which the chemical is absorbed. Tablets containing TEM should be given to patients in a fasting state with water, and perhaps with a buffering alkali, to minimize decomposition before absorption has taken place.

The initial oral dose of TEM should not exceed 2.5 mg. If this amount is well tolerated for 1 to 2 days, the dose may be increased to 5 mg. Although slight loss of appetite or nausea is a common occurrence, the appearance of severe anorexia, nausea, vomiting, or diarrhea indicates overdosage, either from excessively large single doses or from a cumulative effect. The WBC should be determined before each dose is given. When the prevailing count falls abruptly, it is imperative that the administration of the drug be suspended immediately until the hematologic status becomes stabilized. The full effect of a given dose may not be manifest for 10 to 14 days. Anemia or thrombocytopenia rarely develops during prolonged therapy without antecedent depression of the leukocyte count. In the present group of patients serious depression of marrow function resulted from overdosage of TEM in 10 instances. This usually subsided fully
and spontaneously in 2 to 6 weeks, but it may have hastened the death of 2 patients.

Harmful effects of TEM can be avoided only by carefully regulating the amount of the chemical given. If the difference between the toxic and therapeutic doses could be increased by the administration of a compound like cysteine the safety and utility of the chemical would be enhanced.34, 35

Once the initial effects of TEM have been produced and the approximate dose established for a given patient, the problem of maintaining a therapeutic effect and preventing relapse arises. The action of TEM, like that of nitrogen mustard, is transitory. Long remissions in the diseases that respond to this chemical are scarcely to be expected after brief periods of therapy. In most patients continued evidence of disease activity make it necessary to give maintenance doses at intervals no greater than 1 to 2 weeks. TEM seems to be an agent that is well adapted for sustained therapy, apparently differing in this regard from another nitrogen mustard compound (R 48) that has been effective when given by mouth.36 Prolonged remissions have been maintained in some of our patients with doses as small as 1 to 2.5 mg. per week. Others have required as much as 5 mg. twice a week.

How long the administration of TEM should be continued without interruption to obtain the best long-term results in different disease entities is a matter for further study. Our policy has been to maintain treatment for at least 5 to 6 months, even though signs of disease activity may disappear sooner, before therapy is suspended and evidence of relapse awaited. Many patients will probably require the administration of TEM at close intervals, indefinitely.

Deleterious effects from sustained therapy, other than temporary depression of bone marrow function, have not been observed. Patients treated for many months have maintained their optimal body weight, have not shown undue susceptibility to infection and have not developed abnormalities in serum protein constituents.

The availability of a chemotherapeutic agent such as TEM, which can be used with reasonable convenience and safety without cumulative damage to normal tissues, suggests the need for reconsidering some currently accepted opinions regarding the long term management of the chronic proliferative diseases arising from lymphatic tissues. It would appear desirable to suppress the objective manifestations of disease continuously, even in the absence of clinical symptoms, and to prevent, if possible, the development of complications such as bone marrow damage. The extent to which health and longevity can be prolonged by this means is a matter for continued study.

Conclusions

1. Triethylene melamine (TEM) is an important addition to the chemotherapeutic agents useful in the treatment of malignant disease, particularly Hodgkin's disease, malignant lymphoma, chronic lymphocytic leukemia, lymphoepithelioma of the nasopharynx and papillary cystadenocarcinoma of the ovary.

2. TEM may be used advantageously in conjunction with local roentgen therapy, and in situations in which whole body irradiation or P32 has been used.
3. TEM may be the agent of choice in treating chronic lymphocytic leukemia, especially in patients with leukemic infiltration or replacement of the bone marrow.

4. The effective dose of TEM when given by mouth varies greatly from patient to patient. With adequate precautions it can be used without undue risk.

5. TEM appears to be an agent well suited for sustained therapy without the production of cumulative damage to normal tissues.

REFERENCES


R. WAYNE RUNDLES AND W. BRUCE BARTON

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