THE EFFECT OF THIOURACIL ON LEUKEMIA*

By Louis R. Limarzi, M.D., Richard J. Kulasavage, M.D., and Conrad L. Pirani, M.D.

ONE of the toxic reactions of therapeutic doses of thiouracil in the treatment of hyperthyroidism is the development of granulocytopenia. A nonfatal granulocytopenia and a fatal type of agranulocytosis have been reported. The selective action of thiouracil on the granulopoietic tissue is the basis for the present evaluation of the drug in the treatment of leukemia.

The 6 cases studied included 4 of chronic myeloid leukemia, 1 of chronic lymphatic leukemia, and 1 of acute myeloid leukemia.

Hematologic surveys, including sternal marrow examination, were made in each case prior to and at frequent intervals during and after the administration of thiouracil. The method used for obtaining and studying the marrow is described by Limarzi.† The basal metabolic rate and certain blood chemical constituents including uric acid and cholesterol were determined before, during, and following treatment with thiouracil. Creatine balance studies were carried out in 1 case of acute myeloid leukemia during the administration of the drug.

It will be noted in table 1 that the total amount of thiouracil given varied from 1.6 Gm. administered over a period of 8 days to 2.74 Gm. administered in gradually increasing doses over a period of 3 months. The average daily dose ranged from 0.2 Gm. to 3.0 Gm. Thiouracil was without effect on the basal metabolic rate, and the blood chemical findings were not appreciably changed except in case 5. In the patient (case 5) with chronic myeloid leukemia, who developed an extreme neutropenic leukopenia following treatment with thiouracil, the blood uric acid gradually rose to 11.4 mg. per 100 cc. of blood prior to death.

The blood picture and bone marrow (table 2), except in case 5, failed to show any marked change after the administration of thiouracil.

In a 7 year old boy (case 3)‡ with acute myeloid leukemia who received approximately 0.3 Gm. of thiouracil daily for a period of 1 month, there were no changes either in the blood picture or the creatine metabolism.

A case of chronic myeloid leukemia with specific cutaneous lesions (case 2) received a daily dose of 0.2 Gm. of thiouracil for a period of 8 days. The rapid terminal phase with an acute blood pattern ("hiatus leukemicus") was similar.

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† These studies were made possible, in part, through a grant from Armour and Company, Chicago, Illinois.

‡ The thiouracil was supplied through the courtesy of Dr. George R. Hazel of the Abbott Laboratories, North Chicago, Illinois.

§ This case was studied by Dr. H. G. Poncher of the Department of Pediatrics.
to that observed by Paul and Limarzi in a case of myeloid leukemia which had not received thiouracil. At autopsy the hemopoietic, as well as the other organs, showed a general infiltration of tissue by myelogenous cells of all types. There was no morphologic thyroid hyperplasia.

A woman with chronic myeloid leukemia (case 3) was given thiouracil in dosage of 1.7 Gm. daily for 11 days. The drug was well tolerated. Shortly after the drug was discontinued, the patient developed some gingival oozing of blood. The oral bleeding increased with the addition of retinal and conjunctival hemorrhages. Examination of the blood revealed a marked reduction in the platelet count and an increased bleeding time. The bleeding continued and the patient died following a cerebral hemorrhage. This patient’s white cell count fluctuated from day to day during the administration of thiouracil, and 48 hours prior to death the white cell count was estimated at 310,000. The blood and bone marrow examination failed to show any morphologic changes of the granulopoietic elements that could be attributed to the toxic effect of the drug. It is well known that the leukocyte count in cases of leukemia is subject to daily fluctuation and a marked increase in the white cell count at the time of death is known to occur in leukemia. For this reason it is difficult to say to what extent the drug affected the case studied.

A case of chronic myeloid leukemia in a 2.5 year old male (case 4) with a white cell count of 370,000 was first given a series of roentgen treatments over the spleen.

<table>
<thead>
<tr>
<th>Sex and Age</th>
<th>Type of Leukemia</th>
<th>Total Amount of Thiouracil</th>
<th>Days on Thiouracil</th>
<th>Average Daily Dose of Thiouracil</th>
<th>Blood Chemistry (mg. per 100 cc. of blood)</th>
<th>Basal Metabolic Rate</th>
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<tbody>
<tr>
<td>Case 1</td>
<td>Acute myeloid</td>
<td>Gm.</td>
<td>10.0</td>
<td>0.33</td>
<td>3.9</td>
<td>157</td>
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<tr>
<td>Case 2</td>
<td>Chronic myeloid (with specific cutaneous lesions)</td>
<td>1.6</td>
<td>8</td>
<td>0.2</td>
<td>1.9</td>
<td>151</td>
</tr>
<tr>
<td>Case 3</td>
<td>Chronic myeloid</td>
<td>18.8</td>
<td>11</td>
<td>1.7</td>
<td>1.8</td>
<td>190</td>
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<tr>
<td>Case 4</td>
<td>Chronic myeloid</td>
<td>80.0</td>
<td>100</td>
<td>0.8</td>
<td>3.8</td>
<td>200</td>
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<tr>
<td>Case 5</td>
<td>Chronic myeloid</td>
<td>574.0</td>
<td>90</td>
<td>3.0</td>
<td>3.9</td>
<td>224</td>
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<tr>
<td>Case 6</td>
<td>Chronic lymphatic</td>
<td>60.0</td>
<td>75</td>
<td>0.9</td>
<td>4.1</td>
<td>4.6</td>
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Table 1.—Cases of Leukemia Treated with Thiouracil
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<thead>
<tr>
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<td>21</td>
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<td>0.5</td>
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<td>36</td>
<td>34</td>
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<td>0</td>
<td>11</td>
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<td>18.7</td>
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<td>20</td>
<td>10.0</td>
<td>0.5</td>
<td>84</td>
<td>27</td>
<td>32</td>
<td>17</td>
<td>15.0</td>
<td>9.0</td>
<td>3</td>
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<td>3</td>
<td>7.5</td>
<td>3.10</td>
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<td>15.0</td>
<td>0.5</td>
<td>59</td>
<td>24</td>
<td>5.0</td>
<td>0.5</td>
<td>101</td>
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<td>90.0</td>
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<td>37</td>
<td>7</td>
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<td>40</td>
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<td>6</td>
<td>5.5</td>
<td>3.2</td>
<td>170.0</td>
<td>17.0</td>
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<td>75</td>
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<td>7.5</td>
<td>0.5</td>
<td>90</td>
<td>26</td>
<td>30</td>
<td>0</td>
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</tbody>
</table>

**Remarks**

- Case 1: Hyperplastic with "blast" cells. Markedly "blastic" marrow.
- Case 2: Hyperplastic with mod. "blast" cells. Markedly "blastic" marrow.
- Case 3: Hyperplastic—myeloid type.
- Case 4: Hyperplastic—myeloid type.
- Case 5: Hyperplastic—myeloid type.
- Case 6: Hyperplastic—myeloid type.

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The leukocyte count gradually dropped to 12,100, the splenomegaly disappeared, and the clinical condition became improved. The differential blood smear revealed a moderate myeloid immaturity with an increase in the basophils (8.0 per cent) and monocytes (18.0 per cent), and the bone marrow showed moderate myeloid hyperplasia. During the remission of the leukemic process Fowler’s solution was given. After the 21st day the patient showed a relapse, the leukocyte count gradually rose to 445,000, the splenomegaly reappeared, and the clinical condition became worse. The differential blood smear revealed a more marked myeloid immaturity with a further increase in the basophils (12.0 per cent) and monocytes (18.0 per cent), and the bone marrow showed more marked myeloid hyperplasia.

### TABLE 3.—Leukocyte and Differential Blood Counts in a Case of Myeloid Leukemia Who Received 3.0 Gm. of Thiouracil Daily

<table>
<thead>
<tr>
<th>Date</th>
<th>Leukocytes</th>
<th>Percentage</th>
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<td></td>
</tr>
<tr>
<td>2-3</td>
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<td></td>
</tr>
<tr>
<td>2-7</td>
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<tr>
<td>7-3</td>
<td>1,900</td>
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</table>

**Remarks**

- Before thiouracil
- Thiouracil started
- Thiouracil discontinued
- First convolution
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(liquor potassii arsenitis) was begun and the dosage was gradually increased until the patient was taking 15 minims three times a day. The leukocyte count fluctuated between 11,200 and 60,000. Thiouracil 0.8 Gm. daily was begun when the white cell count increased to 90,000 and the drug was continued for about 3 months. While the patient was receiving thiouracil the leukocyte count gradually increased to 300,000 and the spleen became palpable and gradually increased in size. The leukemic symptoms reappeared. The drug was then discontinued. Neither the blood nor bone marrow pattern was affected by thiouracil (table 2).

A man with chronic lymphatic leukemia (case 6) who was under observation for about one year was given thiouracil 0.9 Gm. daily for about 75 days. No significant change was produced in the blood or bone marrow. Several months after discontinuing the drug he developed a deep and ulcerating lesion on the left posterior faucial pillar and complete bilateral deafness. The leukocyte count reached a peak of 2,60,000. Because of the generalized lymphadenopathy and splenomegaly several roentgen ray treatments were administered. Following this, the white cell count dropped to 60,000 and the lymph nodes and spleen decreased in size. The ulcerating oral lesion and deafness remained unchanged. The patient died in another hospital and no autopsy was obtained. There is no definite evidence to suggest that the thiouracil was the contributing factor in producing the ulcerating oral lesions or deafness in this case of lymphatic leukemia. The interval of several months from the time the thiouracil was discontinued speaks more for an exacerbation of the leukemic process.

In a fourth case of chronic myeloid leukemia (case 5) with a leukocyte count of 440,000 a daily dosage of 3.0 Gm. was followed by an extreme leukopenia and unusual changes in the hemopoietic tissues. This case is reported in detail.

**CASE REPORT (CASE 5)**

H. W., a Negro housewife, 50 years of age, was admitted to the hospital on February 4, 1945, with the complaints of prominence of the left upper abdomen, purple spots appearing on her extremities, loss of 15 pounds in weight, and pains in her legs and arms. She had been well until March 1944, when she began to have aches in her thighs. About 3 weeks later elevated purple spots appeared on her legs, and continued to appear and leave. In the following summer she noticed abdominal fullness and enlargement, especially in the left upper quadrant. By the time of admission she had lost 15 pounds, although her appetite was good.

The past history was essentially negative.

Physical examination revealed a well-developed, well-nourished, Negro female not in any apparent distress. Ophthalmoscopic examination revealed a small hemorrhage with a white center in each eye. Anterior and posterior cervical, axillary, and inguinal lymph nodes were enlarged and palpable. The abdomen was rounded and prominent to the left, where the spleen could be palpated extending from the costal margin to the iliac crest, and from the left flank to the right of the umbilicus. It was firm and movable. The liver was not palpable. Raised purpuric areas, as much as 7 centimeters in diameter, were present on the thighs and right calf. The temperature was 97.6°F., the pulse 78, respirations 20. The weight was 115 pounds, the height 66 inches. The blood pressure was 110/76.

The urine had a specific gravity of 1.010 and contained a trace of albumin and a few epithelial cells. On admission the hemoglobin was 10 grams, red count 4,000,000 per cu. mm., and hematocrit 31 per cent. The leukocytes numbered 450,000 per cu. mm., with 1 per cent myeloblasts, 1 per cent promyelocytes, 39 per cent neutrophilic myelocytes, 32 per cent neutrophilic metamyelocytes, 2 per cent basophils, 2 per cent lymphocytes, 7 per cent eosinophils, 2 per cent stabs, 12 per cent polymorphonuclear neu-
trophils, and 2 per cent monocytes. The Wassermann and Kahn tests were negative. Fasting blood glucose was 69 mg., nonprotein nitrogen 40 mg. per 100 cc. Standard urea clearance was 34 cc. per minute. Serum albumin was 3.8 per cent, serum globulin 1.9 per cent, and blood uric acid 2.9 mg. per 100 cc. The basal metabolic rate was plus 44 per cent. An x-ray of the chest showed elevation of both diaphragms, but normal heart and lungs.

Administration of thiouracil was begun on February 7, 1945, 1.0 gram three times daily.

The temperature rose to 103.5° on February 14 and continued to be elevated. Thiouracil was stopped, but no effect on the fever was noted. A blood culture showed no growth. The drug was resumed 3 days after it had been withdrawn, and the temperature gradually returned to normal on February 22.

The hemoglobin gradually dropped to 7 grams with a red blood count of 2,320,000. This anemia was treated with transfusions, to the total amount of 4.5 liters of citrated blood. The hemoglobin at the time of discharge was 13.6 grams. Headache and muscular pains were treated with tablets of aspirin, phenacetin, and caffeine, as needed, to the amount of 100 grains. Two grains of codeine were also administered. The basal metabolic rate was inconstant: plus 44 per cent, plus 33 per cent, plus 54 per cent, plus 41 per cent, and, at the time of discharge, plus 77 per cent. The nonprotein nitrogen rose to 55 and 62.7 mg. per 100 cc., and then declined to 56. The total white count fell to 180,000 by February 26, but rose to 360,000 by the end of March.

Fig. 1. Peripheral Blood Showing Chronic Myeloid Pattern before Thiouracil Administration
The patient was discharged to the outpatient department on April 14, 1945, and returned to the hospital on May 8, 1945. During the interval she continued the thiouracil as before, 1.0 gram three times daily.

On final admission the patient was much weaker and had lost another 13 pounds in weight. The temperature was 99.2°F, the pulse 80, respirations 18, weight 114 pounds. The blood pressure was 90/60. Otherwise no change was noted in the physical examination.

The hemoglobin was 13.0 grams, red cells 4,000,000, white cells 100,000. The uric acid was 3.6 mg. per 100 cc., and rose terminally to 11.4 mg. The blood cholesterol was 224. The basal metabolic rate was plus 36 per cent. Thiouracil was continued at the same dosage as previously.

Epigastric fullness after meals was treated with tincture of belladonna, with some apparent relief. For vomiting the patient was given one dose of cocaine, ¼ grain orally, preceded by ¼ grain of seconal.

On May 18 the thyroid was biopsied. Thiouracil was stopped on May 25 after the patient had received a total of 2.74 grams. The microscopic examination of the biopsied tissue revealed an edematous stroma. The acini were oval or round in shape and varied markedly in size. The colloid stained unevenly and poorly. There was no evidence of hyperplasia or neoplasia.
The anemia required transfusions to the amount of 3 liters. The last blood transfusion was given on May 18. On May 19 the temperature rose to 101°F, and it rose to almost the same level on the succeeding 3 days. Fluoroscopy of the chest revealed some atelectasis of the right lower lobe. The fever subsided spontaneously. The patient had a convulsion on May 24, epileptiform in type, preceded by involuntary winking and tremor of eyelids. She was given ⁴/₅ grain of phenobarbital three times daily, but another convolution occurred on May 25, and was treated with intravenous sodium amytal, 5 grains. Although the winking occurred several times subsequently, convulsions were seemingly prevented by the sub-

![Fig. 3. Peripheral Blood Following Thioracil Therapy. Terminal Blood Picture Showing a Normal Small Lymphocyte and a Basophil.](image)

cutaneous administration of sodium phenobarbital, 1 grain, at such times, until June 11. On June 11 and again on June 12 the patient had convulsions, both of which were treated with parenteral barbiturate. Because the twitchings became more diffuse and frequent, dilantin, 0.1 gram three times daily, was started on June 14. An electroencephalogram taken on June 19 showed no focus of abnormal activity, and no seizure discharges. There was 6-8 per second activity in all leads with rare bursts of 3-4 per second activity. Another convolution occurred on June 25, and again on June 28 and 29. Three convulsions occurred on June 30, one on July 1, three on July 2. She became disoriented and irrational on July 3 and had one convolution. During the early morning of July 5 she had three convulsions despite 3 grains of parenteral sodium phenobarbital.
At the time of readmission the white count was 110,000. On May 19 it had fallen to 60,000. The count of June 8 was 12,700. By July 3 it had fallen to the minimal level, 1,900.

The temperature began to rise on June 28 and reached a maximum of 104° (axillary) on July 5. At no time was there any oral or pharyngeal ulceration, even at the time of exitus.

The patient died in coma on July 5.

**Fig. 4. Bone Marrow after Thioracil Agranulocytosis**

Note the hyperplasia of the myeloblastic tissue

**Autopsy**

(Pertinent Findings)

The body was that of a well-developed, fairly well-nourished, Negro woman who had been dead about one-half hour. There were two ecchymotic areas over the lateral aspect of the left arm.

**Peritoneal Cavity:** The liver edge extended to approximately 3 fingerbreadths below the costal margin on the midclavicular line. The spleen filled the left upper quadrant, reaching the umbilical line. The mesenteric and retroperitoneal lymph nodes were moderately enlarged and rather soft. On section they showed yellowish-brown surfaces.

**Pleural Cavities:** The lymph nodes in the mediastinum were slightly to moderately enlarged, having an appearance similar to those in the abdomen.
Heart: The heart weighed 220 Gm., and was somewhat softened. There was a large area of fibrous thickening of the pericardium over the anterior wall of the right ventricle. There were a few small areas of hemorrhage over the pericardial surface, especially in the region of the right auricle. The subepicardial fat tissue was gelatinous and yellowish-brown in color. The left ventricular wall measured 13 mm. in thickness; the right ventricular wall 2 mm.

Lungs: There were occasional small areas of hemorrhage and atelectasis, especially along the anterior edge.

Spleen: The spleen was markedly enlarged and firm. It weighed 1250 Gm. The external surface was smooth, with a small area which contained fibrous tags. The cut surface presented a dark red color and was rather homogenous. The fibrous reticulum appeared slightly increased. Within the gastrosplenic ligament were a few nodular structures, measuring up to 2 cm. in diameter, which presented on section a structure similar to that of the spleen.

Liver: The liver was moderately enlarged, weighing 2060 Gm. Numerous enlarged lymph nodes were
present at the hilus of the liver. On sectioning, these nodes presented yellowish-brown surfaces with occasional small, hemorrhagic areas.

**Adrenals:** The adrenal glands showed no gross changes.

**Kidneys:** The right kidney weighed 175 and the left 170 Gm. The capsules stripped with ease, revealing a smooth, red-tan surface. On section the cortical-medullary markings were distinct and the cortex appeared somewhat swollen. In one of the pyramids of the left kidney was a small white nodule. The pelvic mucosa of both kidneys presented a few minute hemorrhages. Similar hemorrhages were present in the upper portions of both ureters. The remaining portions of both ureters and the urinary bladder appeared normal.

**Thyroid:** Part of the right lobe was missing, and what remained of thyroid tissue appeared fibrosed. The left lobe of the thyroid was rather small, measuring up to 4 cm. in its greatest dimension.

**Head:** The skull was rather thick. The brain weighed 1300 Gm. and appeared normal on external

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**Fig. 6. Spleen (High Power)**

Abundant granular pigment is clearly visible either free or within macrophages. Practically no leukemic cells can be seen.
inspection. The dural sinuses were free of clots and the accessory sinuses and middle ears showed no gross changes.

Bone Marrow: The marrow of the sternum, ribs, and vertebrae in the lumbar region was rather pale in color and abundant.

![Image](https://www.bloodjournal.org/figure7.jpg)

**Fig. 7. Lymph Node**

There are numerous pigmented macrophages. The sinusoids are dilated and contain numerous leukemic cells.

**Microscopic Examination**

*(Pertinent Findings)*

Liver: The hepatic cells exhibited a moderate degree of cloudy swelling. Within the periporal spaces were small foci of lymphocytes, blast cells, and mononuclear cells with pale vesicular nuclei and distinct nucleoli (RE cells).

Spleen: The architecture was obscured. There were numerous hemorrhagic areas throughout the pulp, which was otherwise markedly congested and contained much granular brown pigment. There was an occasional follicle with degenerating, germinative cells (reticulum cells). The pulp contained small foci
of immature cells and an increased number of reticulo-endothelial cells. Section through an accessory spleen revealed a marked hyperemia. The sinusoids were dilated.

**Lymph Nodes:** There was a diffuse hyperemia and a marked hyperplasia of the reticulo-endothelial cells. Numerous phagocytes with brown pigment were present. Occasional follicles were small and compressed, showing degeneration of the reticulum cells.

**Bone Marrow:** The cells were very numerous, rather homogenous in type, and of the "blast" type. Occasional megakaryocytes and several phagocytic (R. E.) cells were noted. Only occasional polymorphonuclear leukocytes were present.

**Thyroid:** The alveoli were large and filled with colloid. In one area a marked foreign body reaction was noted around suture material.

**Adrenals:** The cortex presented a few areas in the zona fasciculata where the cells were large, swollen, and presented a vacuolated cytoplasm.

**Hypophysis:** There was a marked hyperemia and occasional foci of "blast" cells within the capsule.

**Skin:** There were a few small focal hemorrhages within the derma.

**Brain:** The gross and microscopic examination of the brain was conducted by Dr. Percival Bailey. Except for a few leukemic cells in the vessels, no abnormalities were observed.

**Fig. 8. Bone Marrow Showing Myeloid Hyperplasia of Myeloblastic Type**

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*EFFECT OF THIOURACIL ON LEUKEMIA*

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The final anatomical diagnoses were: (1) chronic myelogenous leukemia with involvement of the bone marrow, liver, spleen (splenomegaly), kidneys, and lymph nodes; (2) agranulocytosis (toxic); (3) multiple petechial hemorrhages of the serosal surfaces; (4) emaciation; (5) brown atrophy of the heart; (6) multiple small areas of foreign body reaction in the lungs; (7) emphysema of the lungs, moderate; (8) cloudy swelling of the myocardium, liver, and kidneys; (9) old surgical cervical incisions (partial thyroideectomy); (10) chronic perisalpingitis, right; (11) multiple accessory spleens; (12) small fibroma of the kidney.

This case (H. W.) is of particular interest from two main aspects: (1) the possible effect of thiouracil on the leukemic process, and (2) on the central nervous system. The typical blood picture of chronic myelogenous leukemia appeared to be profoundly modified by thiouracil to the extent that an extreme neutropenic leukopenia resulted. The terminal blood pattern in this case is not that usually seen in either a spontaneous remission or an acute exacerbation of a chronic myeloid leukemia, and it differs from that repeatedly observed in remissions induced by roentgen-ray treatment or liquor potassii arsenitis (Fowler’s solution). The first effect of thiouracil in myeloid leukemia, as noted in this case, would appear to be a slowing of the rate of proliferation of the granulocytic elements, reflected in the peripheral blood by a gradual decrease in the total white blood count but with no change in the typical chronic myeloid blood pattern. The second result of thiouracil might be one of actual granulocytic destruction. The gradual disappearance of the granulocytes from the peripheral blood and the increase in the blood uric acid to 11.4 mg. support the presence of two independent mechanisms in thiouracil leukopenia and neutropenia in leukemia, i.e. (1) an inhibition of granulopoiesis, and (2) a destruction of granulocytes. At autopsy the spleen was found to be markedly enlarged (1250 Gm.), but microscopically it presented a picture of marked hyperemia of the pulp with only small foci of blast cells, many showing atypical nuclei. Cells of the granulocytic series were also strikingly absent from the bone marrow, lymph nodes, liver, and kidneys. All these organs contained a moderate number of blast cells and presented a distinct hyperplasia of the reticuloendothelial system. The bone marrow, in particular, appeared markedly hyperplastic with the presence of megakaryocytes and a predominance of blast cells. Erythropoiesis was decreased. It is interesting to note that the final differential blood count consisted of 18 per cent myeloblasts, many atypical or toxic forms, 49 per cent lymphocytes, mostly small types, and 33 per cent basophils, both mature and immature forms. There was a complete absence of neutrophils and eosinophils in the peripheral blood. Apparently, the basophils were resistant to the toxic effect of thiouracil. The lungs appeared grossly normal but microscopically presented a large number of small granulomatous lesions of the foreign body type. These were explained on the possibility of aspiration of foreign material and probably were the cause of an episode of fever associated with pulmonary findings about a month before the death of the patient. Finally, the thyroid failed to reveal any change attributable to thiouracil.

The brain on external inspection and on cross section appeared entirely normal. Microscopically, except for the presence of a few leukemic cells in the lumen of the blood vessels, no remarkable changes were noted. From the electroencephalo-
gram made after the appearance of the convulsions, which showed no evidence of localized damage in accessible parts of the cortex and the lack of any morphologic change of note in the brain, it may be assumed that the clinical evidence of the convulsions resulted from the toxic effect of thiouracil on the central nervous system. In this connection the report of Haines and Keating \(^1\) is interesting. These investigators observed in 2 patients with severe recurrent exophthalmic goiter who were treated with thiouracil, toxic disturbances of the central nervous system consisting of myoclonic contractions of various muscles, and at the same time severe somnolence and confusion were present. Subsequent administration of the drug was followed by a resumption of the toxic disturbances of the central nervous system.

**DISCUSSION**

McGavack, Lombardi, and Schwimmer \(^5\) gave thiouracil to 78 patients with thyrotoxicosis and to 40 individuals without thyroid disease. No untoward response of any kind was observed in those individuals who did not have thyrotoxicosis. In those with thyrotoxicosis the toxic or unusual reactions were divided into two groups: (1) Incidental side effects such as rashes with pruritus, relative granulocytopenia, generalized edema or edema of eyes and ankles, diarrhea and dryness of the mouth and excessive thirst; these manifestations of a mild nature usually disappeared without altering the therapeutic regimen. (2) Manifestations of a severe nature which necessitated discontinuance of thiouracil and which included patients who developed severe febrile reactions with chills, generalized aching and widespread urticarial skin lesions, and agranulocytosis. These investigators reviewed the literature and found that of approximately 2,350 patients who had received thiouracil, 10 (0.40 per cent) had developed agranulocytosis and 4 of these (0.16 per cent) died. Fishberg and Vorzimer \(^6\) noted a definite and sudden granulopenia in 20 per cent of their patients and suggested the use of pyridoxine, vitamin B\(_6\), in prophylactic doses of 150 mg. daily by mouth, or 200 mg. intravenously where severe drops in the leukocyte count have taken place.

From the hematologic point of view thiouracil produces two types of blood and bone marrow patterns: (1) Granulocytopenia in which there is a leukopenia, neutropenia, and a monocytosis. Here the monocytes appear to have their origin from the reticulum. The bone marrow is hyperplastic and shows a moderate to marked degree of granulopoietic immaturity. Immaturity is never carried to the stage of myeloblastic involvement. Ulcerating lesions of the oral cavity are not observed. Following temporary discontinuation of the drug, the blood completely recovers. In fact, there may be a temporary leukocytosis immediately following removal of the drug. (2) Agranulocytosis in which there is a severe leukopenia, complete absence of granulocytes including eosinophils and basophils. Here the bone marrow reveals an aplasia of the granulopoietic tissue. Erythropoiesis and megakaryopoiesis are affected very little. There are a few degenerated and atypical myeloblasts, a marked lymphocytic reaction and a relative increase in plasma cells and reticulo-endothelial elements. Pharyngeal ulcerations are frequently observed in thiouracil agranulocytosis. This type of patient usually dies in less than one
week from the first appearance of the ulcerations in the throat and tonsils. There is a complete aplasia of the granulopoietic elements in the bone marrow.

The clinical and hematological course followed by patients who develop thiouracil agranulocytosis is similar to that seen in agranulocytosis due to a number of drugs and chemicals. Plum and Rosenthal have described in detail the pathologic findings in agranulocytosis due to chemicals and many drugs, especially aminopyrine.

A comparison of the histological findings in cases of agranulocytosis described and illustrated by Rosenthal and the thiouracil agranulocytosis in our case of leukemia is interesting. He observed that in the lung, the alveoli were filled with red blood cells, bacteria, some large endothelial cells, and a few lymphocytes and fibrin. There was an absence of granulocytes. The lymph nodes revealed edema and marked hyperplasia of the reticulo-endothelial cells. The spleen, which may be enlarged and resemble the acute splenic tumor of infections, revealed on historical examination a definite hyperplasia of the reticulo-endothelial system. Plasma cells and lymphocytes were present, but no granulocytes. The bone marrow may be aplastic, normal, or hyperplastic. Rosenthal has also observed a reticuloendothelial type of bone marrow. In the aplastic type there is an absence of granulocytes and myeloblasts with a marked increase in the number of lymphocytes which in some instances may take a follicular appearance, and a relative plasmocytosis. A number of investigators have observed marrows in cases of agranulocytosis with numerous myeloblasts and a few myelocytes and rarely a few mature granulocytes. Degenerated myeloblasts have been described by some workers in cases of recurrent agranulocytosis. In the reticulo-endothelial type of marrow a few myelocytes and myeloblasts and a marked hyperplasia of reticulo-endothelial elements are observed.

In comparison, in our case of leukemia that developed the extreme neutropenic leukopenia, the peribronchial tissue contained a few small accumulations of lymphocytes and epithelioid cells with giant cells. There was an absence of leukemic cell infiltration as commonly observed in cases of leukemia. The architecture of the spleen was obscured by numerous hemorrhagic areas throughout the pulp, which was otherwise markedly congested and contained much granular brown pigment. There was an occasional follicle with degenerating germinative cells (reticulum cells), and the pulp contained small foci of immature cells with an increased number of reticulo-endothelial elements. In the lymph nodes a diffuse hyperemia and a marked hyperplasia of the reticulo-endothelial cells were observed. Some follicles were small and compressed and showed degeneration of the reticulum cells. The bone marrow was hyperplastic and consisted mostly of myeloblasts, many atypical, and a number of reticulo-endothelial elements. Granulocytic elements were practically absent. Erythropoiesis was depressed and a few mega-karyocytes were present.

An interesting observation concerns the persistent splenomegaly after the organ had been practically depleted of leukemic cells as noted at autopsy. It is generally agreed that splenomegaly in leukemic states is due for the most part to proliferation and infiltration of leukemic elements. Apparently, hyperemia and hyperplasia
of the reticulo-endothelial elements are major factors in producing an enlarged spleen in chronic myeloid leukemia. This also explains the cause of the enlarged liver in the presence of a minimal leukemic infiltration of the organ.

Astwood first employed thiourea and thiouracil in the treatment of patients with toxic goiter and found that the drug produced complete remission of symptoms and return of the basal metabolic rate to normal in most patients. These antithyroid drugs inhibit the function of the thyroid gland and, as Williams has pointed out, this is true in spite of the fact that they may increase the work of the gland as evidenced by the marked hyperplasia and hypertrophy which they produce in the thyroid. In patients with leukemia treated with thiouracil there is no clinical improvement, the basal metabolic rate remains elevated, and there is no morphologic thyroid hyperplasia.

The most dangerous extrathyroid effect of thiouracil therapy is agranulocytosis. The findings in the blood and bone marrow have been described. The physiopathological mechanism involved in agranulocytosis is not entirely clear. Plum studied the blood and bone marrow simultaneously in recovered cases of agranulocytosis following the administration of aminopyrine. He observed that the myeloblasts, premelocytes, myelocytes, and metamyelocytes gradually diminished after a few days and at the same time there was a relative increase in mature granulocytes. With the severity of the process the more mature granulocytes gradually became completely depleted, and finally in the very severe and fatal cases the marrow was hypocellular. There was no indication of a maturation arrest, but rather, a hypoplasia of immature granulocytes. According to this mechanism of agranulocytosis, the toxic factor affects, first, the granulocytic precursors followed by the mature granulocytes and, finally, a depletion of all granulocytes with no cells being formed. This is reflected by an agranulocytosis in the peripheral blood. Gargill and Lesses also support this thesis and suggest the destruction of leukocytes in the blood stream as a possible mechanism of the leukopenia as discussed by Lawrence. Experimentally, Warren was able to show that thiouracil in 100 mg. per cent concentration induced a small but significant inhibition of respiration of rabbit bone marrow cells, the effect upon the myeloid elements being more striking. The myeloid elements (mostly myelocytes) were found to be more sensitive to the action of the drug than the more mature polymorphonuclear cells found in the peritoneal exudates of rabbits. Attempts to protect the marrow from the depressant action of thiouracil on respiration by adding pyridoxine or dilute liver extract, all yield negative results. This is of interest since these products have been suggested for the prevention of granulocytopenia induced by thiourea and its derivatives.

Williams and his associates have reported detailed studies on the absorption, distribution, and excretion of thiouracil in experiments on rats and man. They found that thiouracil is rapidly absorbed from the gastrointestinal tract and is readily excreted in the urine. With dosages ranging from 0.2 to 1.2 Gm. daily, the concentration of the drug in the blood varied from 0.8 to 6.4 mg. per 100 cubic centimeters, while the daily excretion in the urine varied from 16 to 618 mg. The distribution of thiouracil in different elements of the blood was studied in
4 individuals who had been treated with the substance for several days. In 3 subjects, the blood cells were found to contain about seven times as much as the plasma; in 1 subject the cells contained twice as much as did the plasma. Although the red cells were found to possess two or more times the amount present in the white cells, the average amount of thiouracil per cell was much greater in the white cells than in the red cells. These investigators carried on some interesting experiments on the absorption of thiouracil by blood cells in vitro. Among the cases studied were the leukocytes from the blood of 3 cases of leukemia. Fifty cc. of blood were obtained from each case of acute myeloid leukemia, chronic myeloid leukemia, and chronic lymphatic leukemia. To the blood were added 10 drops of a 2.0 per cent solution of potassium oxalate and enough of a 2.0 mg. per cent solution of thiouracil to make a final concentration of about 4 mg. per cent. The mixture was incubated at 38° C. for 1 hour and immediately thereafter the estimations of thiouracil were begun. They found that the higher the white count the larger the amount of the drug present in the white cells, whether the cells were almost entirely lymphocytes or whether they were granulocytes. Although the average quantity of thiouracil removed by individual granulocytes was greater than that removed by lymphocytes, the latter cells absorbed more of the drug in comparison to their size. The leukocytes of the acute leukemic patient removed the same amount per volume of cells as did the chronic myelogenous leukemia cells, but the amount per cells was less in the former group. The erythrocytes of the leukemic patients did not remove as much thiouracil per volume of cells as did the red cells of the nonleukemic patient. Finally, it was found that the final concentration of the drug in the plasma was less in the chronic leukemic blood than in the non-leukemic blood. These findings indicate that the leukemic cells of both myeloid and lymphatic leukemia are more active in ingesting thiouracil from the plasma than are nonleukemic leukocytes. Further, the erythrocytes are less active than the white cells in the ingestion of thiouracil. A case of chronic lymphatic leukemia who received thiouracil for several days preceding death was found at necropsy to have some of the substance in essentially all the tissues of the body with very large quantities in the bone marrow, greater than that in any other tissue.

It is interesting to note (case 5) that there was an interval of 6 weeks between the onset of extreme leukopenia and the stopping of thiouracil. The gradual and persistent drop in the white blood count and disappearance of granulocytes from the peripheral blood is difficult to dissociate from a cumulative effect and retention of some thiouracil by the large quantity of leukemic tissue. Experimentally, Williams, Kay, and Jandorf have shown that within certain limits the more tissue present, the less the total destruction of thiouracil. This may in part explain the final production of leukopenia and neutropenia after thiouracil was discontinued.

From the blood and autopsy studies in the case reported above there is evidence that the leukemic process was partially altered although the clinical state was not beneficially affected. There was no evidence to indicate that the thiouracil had produced an exacerbation of the process as one frequently observes in cases of acute exacerbation of chronic myeloid leukemia. The terminal blood pattern was that of a chronic myeloid leukemia from which all the neutrophils and eosinophils
had been removed, leaving a relative increase in myeloblasts, basophils, and lymphocytes.

The basophils (mast cells) were apparently unaffected by thiouracil, and in fact became increased during thiouracil administration. A similar type of basophilia is observed in cases of chronic myeloid leukemia in which a remission had been induced with roentgen therapy and liquor potassii arsenitis (Fowler’s solution). The origin and the distribution of the mast cells (basophils) could not be ascertained in this material. It is well known that the basophil granulation is soluble in water and that an adequate evaluation of the morphology of the human mast leukocyte can only be obtained in properly fixed and stained preparations, preferably in films fixed in 100 per cent alcohol and stained in 50 to 80 per cent alcohol thionine stain.

In the past, many agents have been tried in an attempt to influence human leukemia. With the exception of the remissions induced by liquor potassii arsenitis, roentgen therapy, and radioactive substances, all such attempts have uniformly met with failure. My associates and I (L. R. L.) have tried a number of other medical and surgical procedures in cases of leukemia in an attempt to alter the leukemic process. These included aminopyrine, colchicine, and total thyroidec-tomy, the latter in order to produce myxedema and influence the metabolism of hemopoiesis in leukemic conditions. No clinical or hematological improvement of lasting value was noted. Thiouracil may occasionally alter the leukemic process and in so doing produce the other extreme, a neutropenic leukopenia, an effect that is not clinically beneficial. It can be assumed that idiosyncrasy or hypersensitivity does not play a part in thiouracil leukopenia and neutropenia in leukemia.

CONCLUSIONS

1. Thiouracil, which is occasionally productive of agranulocytosis, is of no value in the treatment of leukemia, even when given in very large doses.

2. In one case of chronic myeloid leukemia given 2.74 Gm. of thiouracil for 90 days, an extreme leukopenia developed 6 weeks after the drug was discontinued. The patient developed toxic disturbances of the central nervous system. Both of these effects may have been related to the thiouracil administration.

3. In cases of chronic myeloid leukemia with a high percentage of basophils in the peripheral blood, the basophils appear to be resistant to the toxic effect of thiouracil and in this respect simulate the blood pattern observed in remissions induced by roentgen therapy.

4. Thiouracil in sufficient doses may inhibit granulopoiesis and destroy granulocytes.

REFERENCES

L. R. LIMARZI, R. J. KULASAVAGE, AND C. L. PIRANI

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