expressed in per cent of fasting value is not much affected by decreasing the size of the intravenous dose of insulin below 0.1 u/kg or by increasing it in oneirophrenics. At 15 minutes the separation is statistically valid despite a bump of unknown significance on this descending limb of the curve. Therefore, it is possible, in patients suspected of oneirophrenia, to estimate the resistance to insulin with a statistical validity as great as can be obtained from much longer tests.

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Thiouracil in the Treatment of Leukemia.

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It has been observed that patients with leukemia may show many of the clinical features of hyperthyroidism, such as nervousness, tachycardia, decreased cholesterol in the blood, and increased metabolic rate. Temporary improvement may result from the rational use of Lugol's solution.[1-3]

During the past 15 years, 175 patients with various types of leukemia have been studied in this clinic. The disease remained stationary or progressed slowly as long as the cholesterol level was above 150 mg %, but progressed rapidly when the cholesterol values fell below 100 mg %.

The cholesterol levels appeared to be influenced by the absolute number of extremely immature forms and not by the total number of circulating leukocytes. The cholesterol levels decreased as the number of immature forms increased, but in one group of 15 patients who progressed rapidly to a fatal end, with extensive systemic and visceral myeloblastic proliferation, the total counts were slightly elevated, normal or reduced, and the absolute number of myeloblasts small, yet the cholesterol levels were constantly below 100 mg %.

In remissions induced by X-ray therapy, the serum cholesterol values were uniformly above 150 mg %, and as the patients became resistant to the X-ray, the cholesterol levels fell.

There was no constant relationship between the basal metabolic rate, the serum cholesterol values and the prognosis.

It seemed desirable to determine whether the administration of thiouracil would increase the serum cholesterol levels and improve the patient's symptoms.

Case 1. S.K., white female, age 29 years with chronic myelogenous leukemia. The disease was apparently in its second year when it was recognized in 1940. Between October 1940 and June 1945, she received several series of X-ray treatments. These were given by spray and locally over the spleen. (These treatments totalled 1100 R. by spray and 1950 R. over the spleen). She experienced several striking clinical and hematological remissions. The last X-ray treatment was on June 5, 1945. The subsequent events are summarized in Table I.

This patient received 1.5 g of thiouracil a day over a period of 60 days, or a total of 90 g. She tolerated the drug quite well. She had an irregular, intermittent fever which was present before the administration of thiouracil was begun and persisted thereafter. At first, she seemed clinically improved; she felt stronger and the hemoglobin and red cell levels rose temporarily. The circulating leucocyte count fell precipitately during the first 24 hours after the drug was given, but

[1] Friedgood, H. B., *Am. J. Med. Sc.*, 1932, **183**, 515.

[2] Williams, R. H., and Bissel, G. W., *New Eng. J. Med.*, 1943, **229**, 97.

[3] Atwood, E. B., *J. A. M. A.*, 1943, **122**, 78.

TABLE I.
Temporary Drop in the White Count After Thiouracil in Chronic Myelogenous Leukemia.

Date	Thiouracil g/day	WBC (thous.)	Mature Myeloid C. %	Immature Myeloid C. %	Hgb., g	RBC (mill.)	B.M.R. %	Serum cholest., mg %	Bone marrow WBC (thous.)	Bone marrow Myelocytes, %	Bone marrow Myeloblasts, %
9/10/45	—	400.0	45	35	6.0	3.0	+14	165	274	33	17
11	1.5	*430.0	—	—	6.4	2.0	—	—	—	—	—
12	,,	*109.0	50	44	6.3	—	—	—	—	—	—
13	,,	130.0	—	—	—	—	—	—	—	—	—
14	,,	134.0	59	31	7.2	3.1	—	175	280	42	22
21	,,	170.0	60	31	7.3	2.3	+17	210	—	—	—
28	,,	155.0	39	46	8.3	2.5	+24	220	—	—	—
10/ 3	,,	146.0	45	50	8.6	2.5	+ 8	212	—	—	—
10	,,	120.0	40	52	10.6	3.5	+10	210	—	—	—
11/12	,,	283.0	32	57	7.3	2.3	+14	145	450	28	46

* Checked repeatedly.

there was no corresponding quantitative change in the bone marrow. Furthermore, there was no appreciable change in the maturation pace of the bone marrow elements. The drug did not affect decisively the red cells, hemoglobin or platelets. The basal metabolic rate did not fall to any important extent and the cholesterol level did not change. She grew gradually worse, lost weight, became steadily weaker and the spleen enlarged progressively and rapidly. In mid-November, she developed purpura (platelet count 100,000). It is obvious that thiouracil had failed to decrease the myeloid hyperfunction and leukocytosis and to influence the rate and degree of maturation of the myeloid elements. The patient became resistant to X-ray therapy, failed rapidly and died 7 months later.

Case 2. D.C.L., white female, age 49 years. Chronic myelogenous leukemia diagnosed in 1941. Between July 1941 and July 1945 she received a series of X-ray treatments by spray and over the spleen. (A total of 1150 R. over the spleen and 550 R. by spray). The induced hematological and clinical remissions were satisfactory. The last X-ray treatment before thiouracil was given on January 11, 1945. The subsequent developments are shown in Table II.

This patient received a total of 26.7 g of thiouracil in 15 days. She tolerated the drug quite well and remained afebrile. There was no significant quantitative or qualitative change in the peripheral white blood cell picture or in the bone marrow pattern. The red cell count and hemoglobin value remained unchanged throughout the period of observation. There was no demonstrable increase or depression of red cell formation, nor the platelets influenced. It is apparent that thiouracil, in this patient, failed to depress the basal metabolic rate since at the end of the second week the basal metabolic rate had risen to +47% and the serum cholesterol had fallen materially. A partial remission in the disease was induced by X-ray treatments later on.

Case 3. B.E.D., white male, age 27 years, suffering from myelogenous leukemia of 3

TABLE II.
Negative Effect of Thiouracil on Total White Count in Myelogenous Leukemia.

Date	Thiouracil g/day	WBC (thous.)	Mature Myeloid C. %	Immature Myeloid C. %	Hgb., g	RBC (mill.)	B.M.R. %	Serum cholest., mg %	Bone marrow WBC (thous.)	Bone marrow Myelocytes, %	Bone marrow Myeloblasts, %
7/ 3/45	Received 3 blood	500	38	47	6.4	2.0	+31	205	458	32	6
5	transfusions	346	67	26	8.0	2.2	—	—	—	—	—
9	—	520	50	49	9.0	2.9	—	200	—	—	—
10	1.6										
12	”	515	52	45	9.8	2.9	—	—	—	—	—
15	”	370	36	62	9.7	2.7	—	—	—	—	—
16	1.9										
17	”	445	37	63	8.8	3.1	+32	205	—	—	—
24	”	378	43	56	9.7	3.3	+47	120	383	50	7
25	X-ray begun										
8/ 1		85	81	17	9.1	3.1	—	200	—	—	—

TABLE III.
Striking Failure of Thiouracil in Lowering the Basal Metabolic Rate in Chronic Myelogenous Leukemia.

Date	Thiouracil g/day	WBC (thous.)	Mature Myeloid C. %	Immature Myeloid C. %	Hgb., g	RBC (mill.)	B.M.R. %	Serum cholest., mg %	Bone marrow WBC (thous.)	Bone marrow Myelocytes, %	Bone marrow Myeloblasts, %
8/ 6/45	—	56.0	*61	36	6	1.8	+70	83	250	40	15
7	1.6										
9	”	26.2	*58	32	6	2.0	—	—	—	—	—
13	”	30.0	*63	20	6.9	1.9	+89	70	—	—	—
19	”	37.5	*47	41	6.8	1.8	—	—	215	†38	28

* 25% or more were basophiles.
† Many basophiles.

years duration. He had received a series of X-ray treatments with temporary improvement. The last X-ray treatment was given in December 1944, 8 months before thiouracil was tried. (A total of 1350 R. by spray and 1075 R. over the spleen). The result of thiouracil treatment is summarized in Table III.

It is obvious that thiouracil did not affect the total circulating white cell mass, the bone marrow pattern, the basal metabolic rate or the serum cholesterol. The erythroblastic system was not influenced. This patient's high basophile count was probably due to the prolonged X-ray treatments. Thiouracil, again, did not influence the hemoglobin, red cell or platelet values. This patient expired two weeks later with profuse internal and external hemorrhages.

Case 4. E.M.G., white female, age 40 years. This patient had noticed repeated bleeding into the skin, from the gums, and a progressive abdominal discomfort over a period of one year. She was admitted to the surgical service and the disease was recognized as chronic myelogenous leukemia with striking splenomegaly. She received a series of X-ray treatments by the spray method and over the spleen. (Spray 100 R.; spleen 450 R.) Since she had not received any previous treatments, the patient was considered a suitable subject to test the effect of thiouracil on the X-ray-induced remission in myelogenous leukemia. These observations are shown in Table IV.

It is apparent that thiouracil did not prolong or modify the X-ray-induced remission. She received 359.3 g of the drug in 10 months. The variations in the metabolic rate and serum cholesterol are rather striking, but inconclusive.

Two other patients with chronic myelogenous leukemia were given thiouracil to test the effect of this drug on X-ray-induced remissions. The results were analogous to that described above. It is obvious that thiouracil does not prolong or modify the remissions induced by X-ray treatments.

Thiouracil was given to one patient with an untreated myeloblastic leukemia. He re-

TABLE IV.

Effect of Thiouracil on the Duration of X-Ray Induced Remission in Chronic Myelogenous Leukemia.

Date	Thiouracil g/day	WBC (thous.)	Bone marrow: Mature Myeloid C. %	Bone marrow: Immature Myeloid C. %	Hgb., g	RBC (mill.)	B.M.R. %	Serum cholest., mg %	Bone marrow: WBC (thous.)	Bone marrow: Myelocytes, %	Bone marrow: Myeloblasts, %
6/14/45	—	710	41	54	8.3	2.5	+70	—	575	27	2
	X-ray Px										
	Spray 100										
	Spleen 450										
	R.U. 550										
21	0.6										
26	,,	35.0	63	26	10.5	3.4	—	—	—	—	—
8/29	0.9	9.0	70	1	14.2	4.7	— 6	225	—	—	—
9/ 6	,,	11.0	72	2	14.1	4.9	—	210	—	—	—
27	1.2 to 1.5	6.5	66	2	14.4	4.9	+ 2	320	—	—	—
10/11	,,	9.2	76	6	15.6	4.7	+16	230	—	—	—
11/ 8	,,	7.7	72	9	16.0	5.2	— 1	238	—	—	—
2/ 8/46	,,	115.0	64	33	12.6	4.0	+11	190	—	—	—
3/11	,,	176.0	48	36	14.8	4.5	+33	160	—	—	—
4/ 3	,,	166.0	70	26	13.1	4.2	+19	170	397	28	1

ceived 1.5 g a day. There was no change in the peripheral white cell picture, qualitatively or quantitatively, nor did the bone marrow pattern change. This patient expired on the 15th hospital day of thiouracil treatment.

Discussion and Conclusions. Thiouracil was administered to 6 patients with chronic myelogenous leukemia, and to one patient with an acute myeloblastic leukemia. The dosage averaged 1.5 g a day and was well tolerated by every patient. One patient (case 4) received a total of 359.3 g of the drug over a 10-month period. The drug had no effect on the total circulating white count, nor on the differential white cell picture, red cell elements, hemoglobin or platelet values or the bone marrow pattern.

Recently, and after completion of this study, one observer reported that he had tried thiouracil in doses of 3 mg daily in a patient with myelogenous leukemia without appreciable results.[4]

[4] Limarzi, L. R., Kulasavage, R. J., and Pirani, C. L., *J. Hem. (Blood)*, 1946, **1**, 426.

Thiouracil did not influence the metabolic rate of leukemic patients materially when given in a dose of 1.5 g daily. This was true whether it was administered over a period of 2 weeks, 2 months or 10 months. The serum cholesterol rose in only 2 patients (cases 2 and 4), and this rise was only transitory. In one patient (case 3) the serum cholesterol continued to fall, the basal rate steadily rose despite the administration of thiouracil. In one patient reported (case 4), and in 2 others, this drug failed to prolong or modify the remission induced by irradiation. Thiouracil given in the dosage reported in this series had no demonstrable effect on the myeloid dysfunction, basal metabolic rate, the serum cholesterol level or the bone marrow pattern of patients with myelogenous leukemia.

Thiouracil, furthermore, did not modify the clinical course of the disease. It seems certain therefore, that this drug has no value as an adjunct in the treatment of myelogenous leukemia.

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Effects of Liver Feeding on Growth and Ovarian Development in the Hyperthyroid Rat.*

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It has been demonstrated that excessive doses of thyroxin or desiccated thyroid cause anestrus and loss of body and ovarian weight in the adult rat and prevent gonadal development in the young animal. The deleterious effects in the adult rat according to Drill *et al.*[1] can be prevented by the administration of increased amounts of thiamine or yeast. Such nutrients are without effect, however, in the young animal.[2] It appears, therefore, either (1) that the young rat is more susceptible to the toxic effects of thyroid insofar as gonadal physiology is concerned or (2) that excessive thyroid feeding may precipitate a deficiency of some nutrient other than the above necessary for gonadal development in the immature rat. In the

* The subject matter of this paper has been undertaken in cooperation with the Committee on Food Research of the Quartermaster Food and Container Institute for the Armed Forces. The opinions or conclusions contained in this report are those of the author. They are not to be construed as necessarily reflecting the views or indorsement of the War Department.

[1] Drill, V. A., Overman, R., and Leathem, J. H., *Endocrinology*, 1943, **32**, 327.

[2] Ershoff, B. H., *Endocrinology*, 1945, **37**, 218.