Resistance of Normal Human Thyroids to Propylthiouracil.*† (19913)

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Propylthiouracil in large doses has been administered to 8 euthyroid women in an attempt to induce hypothyroidism and the menstrual abnormalities associated with the hypothyroid state. Although the therapy was continued for 7½ months and the dosage for the last 6 weeks was 3000 mg daily in divided portions, no instances of hypothyroidism or myxedema occurred.

Since thiouracil and thiouracil derivatives are so effective in controlling the hyperactive thyroid, there have been repeated attempts to decrease the activity of the normal thyroid in angina patients where a general decrease in metabolism is desired. Table I recapitulates the literature available on the effectiveness of thiouracil on euthyroid individuals. An interpretation of the table is difficult because of the varying drugs and dosages represented, as well as the varying lengths of administration. The general opinion of the authors cited, however, is that thiouracil will decrease metabolic activity of anginal patients and reduce the frequency of anginal attacks. As can be seen by Table I, approximately ¾ of the patients developed a lowered metabolic rate; 18 of the 93 developed myxedema, a ratio of 1:5. It is interesting to note that in a series similar to the one here reported, 5 of 10 healthy males at Vermont State Hospital developed a lowered metabolic rate while taking thiouracil for 4 months, but none developed myxedema.

Material and methods. 6-n-propylthiouracil was procured as a powder,‡ weighed, and placed in 250 mg and 500 mg amounts in gelatin capsules. Each of the 8 patients received the following course of treatment:

250 mg	alt dei	× 8 days
250	daily	× 7
250	b.i.d.	× 7
250	t.i.d.	× 5
500	b.i.d.	× 6 wk
750	b.i.d.	× 6
1000	b.i.d.	× 6
1000	t.i.d.	× 6

The subjects were patients at the Arkansas State Hospital for Nervous Diseases at Little Rock, Arkansas. For a primary psychiatric diagnosis, 5 had schizophrenia, 2 had mental deficiency, and one had general paresis. Physically, no patient revealed hypothyroidism

TABLE I. Recapitulation of Literature on Effect of Thiouracil Derivatives on Normal Human Thyroids.

Reference	Disease	Total No. patients	BMR decreased	Developed myxedema	Drug*	Daily dose, mg	Duration, wk
Ben-ashur(1)	Angina	37	35	2	T	100–600	?
Dipalma, *et al.*(2)		8	2	2	T	(209 g, 250 days)	
Hollander, *et al.*(3)		10	1	1	Pt	50–200	12–33
Raab(4)		10	7	1	T	100–1200	4–26
Schoenwald(5)		3	3	3	Mt	100–600	?
Reveno(6)		8	6	2	T	200–600	6–33
					Pt	75–125	10–12
Waitzkin(7)		7	7	7	Pt	800–3000	8–40
Raab(8)	10 healthy patients at Vermont State Hosp.		5	0	T	400	16
		93	66	18			

* T = Thiouracil; Pt = Propyl-thiouracil; Mt = Methyl-thiouracil.

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‡ Generously supplied by the Lederle Laboratories.

prior to onset of treatment. In each instance, they had regular, ovulatory menstrual cycles as proven by weekly endometrial biopsies before therapy. Endometrial biopsies were obtained at weekly intervals before, during, and after propylthiouracil therapy. They were taken with a Randall suction curette and stained with hematoxylin and eosin. The letters "P" and "S" on Fig. 1 indicate "proliferative" and "secretory" endometrium, respectively. The character of the endometrium at the time of menstruation is depicted on this chart. A *proliferative* endometrium signifies failure of progesterone secretion, failure of corpus luteum formation, and thus failure of ovulation. A *secretory* endometrium, on the other hand, indicates that ovulation, corpus luteum formation and progesterone secretion have occurred. So "P" indicates an anovulatory cycle, and "S" indicates an ovulatory cycle. Biweekly red blood cell and white blood *cell counts* were made during the administration of the propylthiouracil to guard against idiosyncrasy to the drug. The *basal metabolic rate* was determined at weekly intervals before, during, and after completion of therapy.

Results. The data obtained from a single patient, D.K., are presented graphically in Fig. 1. Of the 96 menstrual cycles observed, only 3 were anovulatory, 2 of these occurring in Pt. D.K. (Fig. 1). All other cycles were regular and ovulatory, as indicated by the

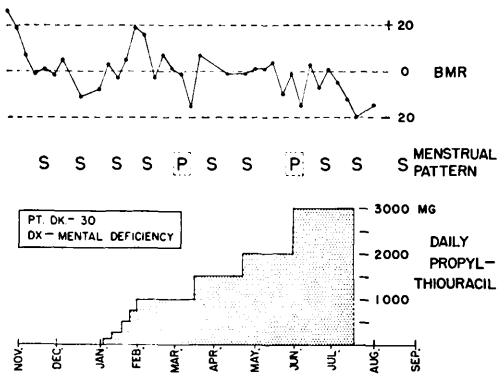

FIG. 1. Graphic illustration of the basal metabolic rate (BMR) and premenstrual endometrial pattern of an individual patient during the control period and while under therapy with the indicated amounts of propylthiouracil. For explanation of the letters "P" and "S," see text.

TABLE II. White Blood Counts during Propylthiouracil Therapy (43-51 Counts/Patient).

Patient	Highest	Lowest	Avg
C.	7500	4500	5450
H.	12400	5400	7800
L.H.	12200	4300	6850
L.	15800	4100	5150
B.	13800	5000	7650
S.	15300	7000	11400
K.	13800	4500	8200
W.	11000	4700	6700

endometrial biopsies. Correlating the propylthiouracil administration with the basal metabolic determinations, it may be seen that a plateau was reached before administration of the drug which was not significantly altered by the drug (Fig. 1).

A summary of the white blood cell counts is shown in Table II. In no case was a leucopenia found, although the biweekly determinations showed a rather wide variation. Fig. 1 shows minimal and maximal values, along with the mean value for each patient. The red blood cell determinations showed no changes of significance.

Discussion. In the majority of smaller experimental animals, guinea pigs, rats, mice, etc., hypothyroidism is easily induced in the normal animal by adding small amounts of thiouracil or its derivatives to the diet. According to the literature on man, about ¾ of euthyroid patients who receive therapeutic amounts of thiouracil develop clinical hypothyroidism and about one-fifth are said to develop myxedema.

With this in mind, 8 women were selected, because of the regular occurrence of ovulatory menstrual cycles as proven by weekly endometrial biopsies, and because of the absence of any signs of hypothyroidism, to be subjects to receive propylthiouracil in an attempt to induce hypothyroidism and precipitate menstrual abnormalities associated with the hypothyroid state. Propylthiouracil was administered in increasing doses from 250 mg to 3000 mg daily over a period of 7½ months, and was accompanied by no clinical evidence of hypothyroidism, no consistent alteration in the basal metabolic determinations, and no alteration in the menses of any of the 8 subjects. The occurrence of 3 anovulatory cycles

among the 56 occurring during therapy was interpreted as probably a normal occurrence unrelated to the drug. No toxic manifestations occurred in these patients, in spite of the high dosages of propylthiouracil utilized.

To verify that these psychiatric patients received the correct amounts of the propylthiouracil, it was dispensed by one of the authors personally. On 3 occasions, one of the patients vomited the material; this happened so infrequently, it was felt that it did not affect the final outcome of the observations.

None of the patients developed clinical manifestations of hypothyroidism. No palpable enlargement of the thyroid was noted. On the other hand, the attendants at the institution voluntarily offered the information that there was an increased activity and cooperation on the part of the study patients, which may be attributed to the increased attention they were receiving.

In view of the observations of Waitzkin(7), it is possible that the reason for the resistance to propylthiouracil noted in these patients lies partly in the fact that a 12-hour interval lapsed between doses. His patients reached the myxedema level when they received the drug at 6-hour intervals.

Summary. Propylthiouracil was administered to 8 euthyroid women over a period of 7½ months in large dosage. No evidence of hypothyroidism was noted, *i.e.*, no change of basal metabolic rate, no alteration of menstrual cycles, no clinical signs or symptoms of hypothyroidism, and no thyroid enlargement. No toxic manifestations were noted, even though during the final 6 weeks, each patient received 3000 mg of propylthiouracil daily in divided doses.

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Survival, Respiration and Morphology of Sarcoma-37 Cells Exposed to Liquid Nitrogen.* (19914)

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The survival of a variety of cells, tissues, and organisms exposed to subzero temperatures is well known. Reviews of some of the basic technics, results and theories pertaining to survival at low temperatures have been presented by Luyet and Gehenio(1), Luyet(2), Billingham and Medawar(3), and Parkes(4). In general it has been demonstrated that some of the deleterious effects of freezing can be avoided by ultra-rapid cooling and rewarming, by partial dehydration, and by pretreatment with hypertonic solutions of substances such as sucrose, glucose, ethylene glycol, and glycerol. The production of tumors *in vivo* from frozen tumor material has been known for almost 50 years, but the question of the actual survival of frozen tumor cells as opposed to the survival of a virus-like causative agent has been reemphasized(5). The survival of various types of tumor cells following freezing has been recently demonstrated by Walsh, Greiff, and Blumenthal(5), Ludwin (6), and Passey and Dmochowski(7). Walsh *et al.*(5) have observed a decrease in the growth potential of sarcoma-37 cells frozen at —30°C and —70°C, but not when frozen at —190°C and stored at —70°C.

It has been our aim to attempt a quantitative estimation of surviving cells by measuring

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