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The Influence of the Antithyroid Drug, Propylthiouracil, on Reproduction In Rats[1]

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Abstract. The antithyroid drug, propylthiouracil (PTU), when fed to white rats at the dietary level of 0.1 percent PTU in finely ground laboratory chow for ten weeks prior to mating, does not affect the ability of either male or female rats to reproduce. All metabolic evidences examined indicate a lower metabolism under the influence of PTU. The PTU dietary treatment was ceased at conception of PTU females. Characteristics of the offspring did not differ from those produced by mothers maintained on normal laboratory chow throughout the experiment.

The antithyroid drug, propylthiouracil (PTU), has not been as extensively studied as many of the other antithyroid compounds, especially thiouracil. However, it is known that PTU is considerably less toxic than thiouracil and other of the thiouracil compounds (Williams, 1955). With particular reference to the reproductive tract of white rats, little is known of the effects of propylthiouracil treatment with the exception of a recent report (Fregly and Hood, 1959) that both 0.06 percent and 0.1 percent diets significantly increased the testes weight/body weight ratio of normal male rats over that of untreated normal rats. The enlargement was described as true hypertrophy and not due to water accumulation. Similar previous results reported for surgically thyroidectomized rats (Hess, 1953) also indicate relationship between the absence of thyroid hormones and testes size. The significance of the enlargement is not known. Because of this uncertainty and because of the diversity of opinion among investigators about the role of the thyroid in reproduction (Peterson *et al.*, 1952), it seemed worthwhile to study the effects of PTU on various physiological phenomena associated with the reproductive tract. Specifically, the research was directed to the study of the ability of male and female PTU treated rats to conceive, the regularity and length of the estrus cycle and length of gestation in female rats treated with PTU until conception, and characteristics of offspring produced, *i.e.*, litter size, average weight of offspring, growth rates and survival.

METHODS

Twelve male and forty-three female rats of the Holtzman strain,

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age 84 and 111 days, respectively, at the beginning of the experiment, were used. Six males and twenty-two females were fed 0.1 percent PTU[3] mixed thoroughly in finely ground Purina laboratory chow by means of a mix-master. Six males and twenty-one females were fed the finely ground chow without the drug. All animals were given tap water to drink. The type fluid containers and spill-proof food containers used have previously been described (Fregly, 1955). Animals were kept in individual cages in a thermoregulated room maintained at $25 \pm 1°$ C. and illuminated as closely as possible from 8:00 A.M. to 5:00 P.M. Daily body weights of all twelve male animals and thirty-one females (fifteen normal diet and sixteen PTU diet) were recorded as well as daily food and fluid consumption measurements. The weight displacement method was used for the latter determinations. Colonic temperatures in degrees C. were recorded weekly for ten male animals (five normal and five PTU) and nine females (four normal and five PTU), as were oxygen consumption measurements in cc.0_2/100 gms. body weight/hour. The procedure outlined by D'Amour and Blood (1954) was used for the oxygen consumption determinations. In the morning and late afternoon vaginal smears of thirteen normal diet and sixteen PTU diet females were examined microscopically so as to evaluate the regularity and mean length in days of the estrus cycle. In addition, wheel-type activity cages[4] were used to evaluate the regularity and length of the estrus cycle of seven normal and eight PTU animals. Revolutions per day were noted at 8:00 A.M. and the period of the estrus cycle recorded as the time in days between peaks of running activity (Wang, 1924).

At the end of a ten-week experimental period the animals were mated as follows: normal females with normal males; normal females with PTU-treated males; PTU-treated females with normal males; and PTU-treated females with PTU-treated males. Males were placed with females in heat at 6:00 P.M. and removed early on the succeeding day. The females were examined for evidence of sperm, and if sperm were found conception was arbitrarily timed at midnight.

Upon conception, normal and PTU females were placed in individual maternity cages or other suitable cages and PTU females placed on a diet of normal ground chow for their gestation and lactation periods.

During the 11th week, ten females (five PTU and five normal), and during the 11th week and the early part of the 12th, ten males (five PTU and five normal) were sacrificed by ether inhalation and

[3]6-n-propyl-2-thiouracil, Nutritional Biochemical Co., Cleveland, Ohio.

[4]George H. Wahman Co., 1123 E. Baltimore Street, Baltimore, Maryland.

autopsied. Gonads, heart (drained of blood), kidneys, adrenals, thyroids, uteri, seminal vesicles (drained of fluid), prostate and thymus glands were carefully trimmed of excess fat and connective tissue and weighed. Tared pieces of each organ were dried to constant weight. An analytical balance was used. Organ weight/body weight ratios and the percent water of each of the organs were calculated.

Upon birth of the litters, the gestation periods were calculated and the average litter size and average weight of the young at twenty-four hours determined. Maternal care was assessed and survival rates of litters noted. After the young were weaned at the end of a three week lactation period, growth rates of males and females were determined for a period of five weeks.

Results

Male and female rats fed 0.1 percent PTU for ten weeks had lower growth rates, food intakes, oxygen consumption rates, and colonic temperatures, as indicated in Table 1. This table does not include data from all animals but only those for which weekly colonic temperatures and oxygen consumption measurements were taken. An examination of the data for the excluded animals shows similar results.

Table 1

Effect of 0.1 Percent Propylthiouracil (PTU) Diet on Various Metabolic Conditions

Experimental Condition	No. of Rats	Initial Mean Body Weight (Gms)	Final Mean Body Weight (Gms)	Percent Increase in Body Weight	Daily Food Intake (Gm./100 Gm. B.W./day)
Male Rats					
Normal Diet	5	304.8	425.5	38.6	6.1±.10[1]
0.1% PTU Diet	5	294.6	344.3	16.9	5.9±.17
Female Rats					
Normal Diet	4	227.5	289.0	27.0	6.9±.17
0.1% PTU Diet	5	248.0	273.7	10.4	6.3±.23*

	0_2 Consumption (cc/100 gm B.W./hr)[2, 3]	Colonic Temperature Degrees C.[4]
Male Rats		
Normal Diet	113.4±8.1	37.5±.06
0.1% PTU Diet	86.9±4.0*	36.9±.07*
Female Rats		
Normal Diet	119.5±7.7	37.6±.09
0.1% PTU Diet	91.9±6.8*	37.0±.05*

[1]The ∓ values are the standard errors of the means
[2]Corrected to standard conditions
[3]Values measured during 9th week
[4]Values measured during 10th week
*Difference from Normal Diet Group Significant ($P<.05$)

The organ weight/body weight (B. W.) ratio data, although not tabulated here, revealed a higher testes/B. W. ratio in PTU males, higher thyroid/B. W. ratios in both male and female PTU animals, and lowered kidney weight/B. W. ratios in male and female PTU animals. The data on percent water of tared pieces of organs showed good agreement upon comparison of normal and PTU animals. The organ weight/body weight ratios and percent water data compare favorably with results obtained by those investigators who have done more extensive work in the field (Fregly and Hood, 1959).

It is apparent that propylthiouracil as studied in this experiment had an antithyroid effect in that the various aspects of metabolism which were measured were lowered, and in that the drug acted in a goitrogenic capacity as evidenced by the larger thyroid weight/B. W. ratios in PTU treated animals (approximately 3.5x for females and 4x for males).

As noted in Table 2, the mean estrus cycle time as determined by either the vaginal smear or activity cage technique was in good agreement for control and PTU diet animals. Further, there was good agreement between the two techniques. The regularity of the cycle was not affected by propylthiouracil treatment. However, the

Table 2

Estrus Cycle of Control and Propylthiouracil Treated Animals

Control			0.1 Percent PTU Diet		
Rat No.	Mean Length of Activity Cycle (days)	Mean Length of Estrus Cycle[1] (days)	Rat No.	Mean Length of Activity Cycle (days)	Mean Length Estrus Cycle (days)
13	4.6		16	4.0	3.4
15	4.8		17	4.0	3.7
14	4.0	3.9	67	4.2	4.5
35	4.8	5.1	48	5.6	4.3
36	4.8	5.3	49	4.5	4.8
37	5.2	4.2	50	5.0	4.9
7	5.0	4.7	46	3.6	4.3
8		4.0	45	5.5	4.9
9		3.8	41		4.7
10		4.4	42		4.8
11		3.8	43		4.3
12		3.5	44		4.6
32		4.8	47		3.7
33		5.0	38		4.5
34		4.0	39		4.5
			40		4.6
	—	—		—	—
Mean	4.7	4.4		4.6	4.4

[1]Vaginal smear technique

average number of revolutions turned per day by PTU animals was less than that for control animals. This would be indicative of lowered metabolism.

In Table 3 the results of the various matings are shown, as well as the calculated gestation periods. PTU does not appear to affect the

Table 3

Comparison of Reproductive Ability of Normal and PTU Treated Rats[1, 2]

Groups	No. of Females in Group	No. of Females Successfully Mated	Mean Gestation Period (days)[3]
Normal Females with Normal Males	8	7	22.4
Normal Females with PTU Males	8	8	22.6
PTU Females with Normal Males	9	9	22.6
PTU Females with PTU Males	8	7	22.8

[1]PTU females placed on normal diet at conception
[2]Summary of two experiments
[3]Based on 5 animals in each group in which conception was assumed to have occurred at 12:00 a.m. of the day a sperm plug was detected

ability of either male or female rats to reproduce. In view of the uncertainty of the timing of the gestation period it is difficult to judge whether this is affected. Both normal and PTU females prepared nests well before the time of parturition. No difficulties in delivery were noted.

Characteristics of the offspring are grouped in Table 4. There are

Table 4

Comparison of Litter Size and Body Weight of Offspring of Normal and PTU Treated Rats

Groups	Average No. of Rats/Litter	Average B.W. of Rats at 24 hours (Gms)	Average No. of Rats/Litter at 24 hours	Average No. Rats/Litter at end of 3 weeks
Normal Females with Normal Males	9.3	6.5	7.9	7.6
Normal Females wtih PTU Males	8.5	6.4	8.1	7.9
PTU Females with Normal Males	7.8	6.3	7.3	7.1
PTU Females with PTU Males	8.0	6.5	7.1	7.0

no apparent differences among the various groups with the exception that PTU treatment for female rats results in a slightly lower average litter size. The young rats of all groups appeared perfectly normal, and PTU- and normal-diet mothers took equally good care of their young.

The growth rates of the offspring of the various matings are found in Table 5. The offspring grew equally well in all cases.

Table 5

Growth Rates of Offspring of Normal and PTU Treated Rats

Groups	Average Body Weights Beginning of 4th Week Males	4th Week Females	6th Week Males	6th Week Females	9th Week Males	9th Week Females
Normal Females with Normal Males	58.4	52.7	128.6	125.1	263.5	198.1
Normal Females with PTU Males	65.1	51.3	129.6	108.6	265.4	181.8
PTU Females with Normal Males	52.0	50.0	132.0	125.2	266.1	209.6
PTU Females with PTU Males	64.5	62.7	143.5	130.7	285.0	188.0

Discussion

The antithyroid drug, propylthiouracil, does not appear to affect the ability of young male rats to reproduce despite clear evidence of lowered metabolism. This would suggest that the enlarged testes of PTU-treated rats cannot be associated with impotence. According to Fregly and Hood (1959), it is possible that PTU increases output by the pituitary of gonadotrophic hormone or that the sensitivity of the testes is increased to normal gonadotrophin titer. A study indicating characteristics of gonadotrophic hormone would be informative, as would one involving the feeding of PTU to hypophysectomized animals. The increase in size of testes is apparently not accompanied by an increased secretion of testicular hormone since the accessory sex glands do not hypertrophy with PTU administration, nor is there a kidney hypertrophy (Fregly and Hood, 1959) which always accompanies increased testicular secretion. It is interesting that thiouracil does not have any effect on the testes weight to body weight ratio (Williams *et al.*, 1944). The effect of longer term treatment with PTU is needed to further assess the role of this drug in reproduction capabilities of male rats.

In female PTU-treated rats, there do not appear to be any harmful effects of administering the drug up to the time of conception unless it be a slightly lower average litter size. This again is despite the fact that characteristics of lowered metabolism are clearly manifested by PTU treatment. Certainly there were no effects on the length and regularity of the estrus cycle. On the other hand, thiouracil does have a disturbing effect on both of these with consequent lowering of the ability to conceive. Mann (1945) demonstrated that the addition of 0.1 percent thiouracil to the normal diet resulted in the disruption of rhythmic pattern of activity, and an increase in the length of periods between cornification of vaginal mucosa. Barker (1949) reported a marked reduction in fertility in adult female rats which were fed 0.2 percent thiouracil for 10 weeks. In a

study with adult female guinea pigs (Peterson *et al.*, 1952) it was reported that cyclic activity, as indicated by the frequency of vaginal openings in animals treated with 0.1 percent PTU solution in ammonia for seven months, was not significantly affected and further that no sterile animals resulted from the treatment. PTU was without effect on reproduction in female guinea pigs except for a condition of the young which was characterized by extremely enlarged thyroids. This was attributed to the placental passage of PTU (Peterson and Young, 1952). The rats produced in Barker's experiment (1949) also had enlarged thyroids.

In recent renal hypertension experiments (Fregly, 1958) it has been demonstrated that PTU, which lowered blood pressure in rats, does not act as a 'cure' for hypertension, since within two weeks after its withdrawal hypertensive blood pressure levels are reached. Thus it would appear that the effects of PTU are relatively short-lived, and it is conceivable that there is little placental passage of PTU during even the early stages of gestation if treatment is ceased at conception.

It is possible that PTU treatment continued over the period of gestation will have an effect on reproduction in rats, and further, that lactation under continued PTU administration will be detrimental to offspring. Because of possible effects of PTU on the posterior pituitary gland the milk let-down factor (oxytocin) which comes from that gland could be affected. A series of experiments involving continued PTU administration through gestation and/or lactation, as well as administration of PTU to normal diet rats during gestation and/or lactation, is now in progress.

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