Proceedings of the Iowa Academy of Science

Volume 69 | Annual Issue Article 95

1962

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The Influence of the Antithyroid Drug, Propylthiouracil, on Gestation and Lactation in Rats[1]

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Abstract. The anti-thyroid drug, propylthiouracil (PTU), when fed to female rats at the dietary level of 0.1% has a slight effect on the average number of young per litter if administered during the preconception period or gestation but if administered continuously during these periods results in a much lower litter size. PTU treatment of mothers during lactation results in cretin-like young and poor survival rates during lactation and after weaning. Ratios of thyroid weight to body weight indicate transfer of PTU to young during gestation and lactation.

The role of the thyroid gland in reproduction is incompletely understood. A recent report (Cook, 1960) indicated that the ability of white rats to produce viable sperm and to conceive is unaffected by administration of the anti-thyroid drug, propylthiouracil (PTU) during a 10-week preconception period. The administration of the PTU until mating failed to influence the duration of the gestation period, the number of offspring per litter, average weight of offspring, growth rate, and survival. The drug was also without effect on the regularity and length of the estrus cycle in female rates. However, propylthiouracil did have an anti-thyroid effect since oxygen consumption, colonic temperature, food intake, and body weight measurements of experimental animals were significantly lower than those of con-

[1] Supported by grant A-2158 (A) from the National Institute of Arthritis and Metabolic Diseases and by a grant from the Iowa Heart Association.
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trols. The drug also had a goitrogenic effect in that significantly enlarged thyroid glands were produced in treated animals. Thus it would appear that hypothyroidism failed to influence the ability of male and female rats to conceive and that adverse effects were absent in the young of PTU-treated parents whose treatment with the drug did not extend beyond the time of conception.

The present study was undertaken to get more information on the effects of PTU administration to female rats during preconception and on the influence of its administration during gestation and lactation. Characteristics of offspring produced were studied, e. g., litter size, average weight, growth rate, survival, and organ weights. It was not deemed necessary to study further the effects of PTU on male rats since 22 weeks of PTU treatment had failed to affect the ability to impregnate normal-diet females (Cook, 1961).

Methods

Experiment I

Twenty-two male and 53 female rats of the Holtzman strain, age 84 and 111 days, respectively, at the beginning of the experiment, were used. Seven males and 40 females were fed 0.1% PTU[3] mixed thoroughly in finely ground Purina laboratory chow. Fifteen males and 13 females were fed finely ground chow without the drug. All animals were given tap water to drink. In this experiment, as in all the experiments, animals were kept in individual cages in a thermoregulated room maintained at 25±1°C and illuminated from 8:00 AM to 5:00 PM. Body weights were measured weekly. Oxygen consumption measurements (cc 0_2/100 gms body weight/hour) were made during the tenth week of the experimental period on six male and 11 female PTU-treated and on six male and eight female normal chow animals. The procedure outlined by D'Amour and Blood (1954) was used for determination of oxygen consumption. Food containers were removed from the cages for a period of 24 hours prior to the O_2 consumption measurement. Vaginal smears of female animals were taken and examined microscopically so as to not measure their oxygen consumption during estrus.

At the end of a ten-week experimental period 33 PTU-treated and six normal diet females were mated with normal males. Males were placed with females in estrus at 6:00 PM and removed early the next day when the females were examined for evidence of sperm. Food containers were removed from cages

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

during mating so that male animals would not have access to propylthiouracil.

Upon impregnation, females were again placed in individual cages. All normal diet and seven PTU-treated animals were given a diet of ground chow without the drug for their gestation and lactation periods. Seven PTU-treated animals were placed on normal chow during their gestation period but returned to PTU diet during lactation. Nine PTU-treated animals were continued on PTU during their gestation period but placed on normal chow during lactation. Ten PTU-treated animals were continued on the drug for both the gestation and lactation periods.

During the 11th week, 14 females (seven PTU-treated and seven control) and 14 males (seven PTU-treated and seven control) were sacrificed by ether inhalation and 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 on a Roller-Smith torsion balance.

Average litter size was determined at birth. Average weight and litter sizes were determined at 24 hours after birth. Survival rates were noted and average weights of the litters measured at the end of each complete week during a 22-day lactation period.

On the 23rd day after birth some young from each of the five groups in the experiment were sacrificed by ether inhalation. Thyroids, adrenals, gonads, kidneys, and heart (drained of blood) were weighed on a torsion balance. The remaining young were continued on the same diet their mothers had been on during lactation.

Four mothers of each of the five groups in the experiment were sacrificed by ether inhalation on the 23rd day after parturition. Mammary glands were removed and weighed on an analytical balance. Animals were sacrificed after a period of nursing their young.

Experiment II

Six female rats of the Holtzman strain, age 85 days at the beginning of the experiment, were used. Three of the animals were fed a 0.1% PTU diet during their preimpregnation (10 weeks), gestation, and lactation periods. The other three animals were given finely ground Purina without the drug during all three periods. Mating was with normal-diet males. Twenty-four hours after birth, five young from a normal-diet female and six from a PTU-treated female were sacrificed by ether inhalation and their thyroid glands weighed on a torsion balance. The

remaining litters were switched, i.e., PTU-treated mothers were given young from normal-diet animals and normal-diet mothers were given young from PTU-treated animals. Each litter was switched to a foster mother before 48 hours after birth had elapsed. Survival rates and average litter weights were determined at the end of each week for three weeks. The young were then sacrificed by ether inhalation and their thyroids removed and weighed.

Experiment III

Ten males and 29 females of the Holtzman strain, age 85 and 111 days respectively at the beginning of the experiment, were used. All animals were placed on a finely ground Purina laboratory chow diet for ten weeks. At the end of the experimental period mating was carried out as described in the first experiment.

Upon impregnation, females were placed in individual cages. Seven animals were continued on normal chow for both the gestation and lactation periods. Eight animals were continued on normal chow during gestation but switched to 0.1% PTU diet during gestation. Seven animals were given 0.1% PTU diet during gestation but returned to normal chow during lactation. The remaining seven animals were given 0.1% PTU diet during both gestation and lactation periods.

At birth of the litters, the experimental procedure followed was the same as in Experiment I. Average litter sizes were determined at birth, average litter sizes and weights at 24 hours, and survival rates and weekly average body weights throughout the lactation period. On the 23rd day after birth some young from each of the four groups in the experiment were sacrificed and organs weighed. Remaining young were continued on the same diet their mothers had been on during lactation and survival rates noted and average body weights measured for two weeks. Four mothers of each of the four groups in the experiment were sacrificed by ether inhalation on the 23rd day after parturition. Mammary glands were removed and weighed on an analytical balance.

Experiment IV

Eight females of the Holtzman strain were used. Two animals were fed normal chow during the preimpregnation and gestation periods, two were fed 0.1% PTU during a 10-week preimpregnation period and normal chow during preimpregnation gestation, two were fed normal chow during preimpregnation and PTU during gestation, and two were fed PTU during both the preimpregnation and gestation periods. All animals were mated with normal males. At birth, three young from each

group were selected at random, sacrificed by ether inhalation at approximately 24 hours and autopsied. Thyroid gland weights only were measured on a torsion balance.

Results

Experiment 1

Male and female rats fed 0.1% PTU for ten weeks had lower growth rates and lower oxygen consumption rates than animals on normal diet as indicated in Table 1. Thus the anti-thyroid effect of the drug was clearly manifested.

The organ-weight to body-weight (B.W.) ratio data, although not tabulated here, revealed a higher testes to B.W. ratio in PTU-treated males, higher thyroid to B.W. ratios in both male and female PTU-treated animals, and lowered kidney weight to B.W. ratio in male and female PTU-treated animals. The organ-weight to body-weight ratios compare favorably with results obtained by others (Fregly and Hood, 1959).

Table 1. Effect of 0.1% Propylthiouracil (PTU) Diet on Body Weight and Oxygen Consumption.

Experimental Condition	No. of Rats	Initial Mean Body Weight (Gms)	Final Mean Body Weight (Gms)	% Increase in Body Weight	O_2 Consumption (cc/100 gm B.W./hr.)[1,2]
Male Rats					
Normal Diet	6	278.6	411.2	45.4	111.4±2.8[3]
0.1% PTU Diet	6	284.6	322.8	13.4	90.1±3.9*
Female Rats					
Normal Diet	8	212.6	251.0	18.1	122.8±6.2
0.1% PTU Diet	11	217.5	229.9	5.7	91.4±7.6*

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

In Table 2, the results of PTU treatment during various combinations of preimpregnation, gestation, and lactation are shown. It is apparent that PTU treatment during the impregnation period had but a slight effect on litter size but that continued treatment during the gestation period significantly lowered the litter size. In three cases, continued treatment with PTU during the gestation period resulted in stillborn litters.

Table 2. Comparison of Reproductive Ability of Normal Rats and Rats Treated with PTU During Various Periods.

Treatment During			No. of	No. of Females	Average	Average No. of	Average B.W. of
Precon-ception	Ges-tation	Lac-tation	Females in Group	Successfully Mated	No. of Rats/Litter	Rats/Litter at 24 Hours	Rats at 24 Hours (Gms)
.....	.....	.....	5	5	9.4	9.1	6.7
PTU	.....	.....	7	6	8.3	8.1	6.7
PTU	.....	PTU	7	7	7.7	7.6	6.8
PTU	PTU	.....	9	8[1]	4.7*	4.6	6.6
PTU	PTU	PTU	10	10[2]	4.9*	4.9	6.4

[1] One litter of 4 stillborn.
[2] Two litters of 5 each stillborn.
* Excludes stillborn litters.

In Table 3, the average body weights of offspring measured at 24 hours and at weekly intervals are tabulated. Regardless of the treatment during preimpregnation and gestation, PTU treat-

ment during the lactation period resulted in a decreased growth rate. The appearance of these animals was cretinous. They had small, tiny eyes and rough fur. Their movements were sluggish and awkward, and they were not able to raise their hind legs to reach the rest of their body. The testes did not descend.

Table 3. Average Weights of Young Resulting from Normal Rats and PTU Treatment During Various Periods; % of Survival at Three Weeks.

Treatment During			Average Body Weights (Gms) of Young at End of				
Precon-ception	Ges-tation	Lac-tation	at 24 Hours	1st Week	2nd Week	3rd Week	% Survival at 3 Weeks[1]
.....	.....	.....	6.7	15.6	35.0	60.2	97
PTU	.....	.....	6.7	15.5	31.0	57.3	100
PTU	.....	PTU	6.8	14.2	25.0	30.6°	88[2]
PTU	PTU	.....	6.6	13.3	29.9	47.5	100
PTU	PTU	PTU	6.4	15.1	23.6	26.4°	94[2]

[1] Compared to average no. rats/litter at 24 hours.
° Cretins
[2] All animals died after weaning.

After weaning, these animals died. PTU treatment during gestation followed by a normal chow lactation period in mothers resulted in animals smaller than controls but otherwise perfectly normal. These animals survived weaning.

Table 4 shows the organ-weight to body-weight ratios of young taken from each of the groups of Experiment I. The effect of PTU treatment during gestation shows a slight increase of thyroid-weight to body-weight ratio when compared to no treatment with PTU during gestation, and a large increase in thyroid-weight to body-weight ratio when PTU was given during lactation. The high thyroid-weight to body-weight ratios were found in cretinous animals. The testes-weight to body-weight ratios were greatest for young whose mothers had not had PTU during gestation or lactation, next greatest for animals whose mothers had PTU during gestation and not lactation, next greatest for offspring of mothers who had PTU during lactation but not gestation, and least for animals whose mothers had PTU during both gestation and lactation. The kidney, heart, adrenal, and ovary organ-weight to body-weight ratios did not show any trends.

Table 4. Organ-Weight to Body-Weight Ratios (mg/gm body weight) of Some Young of Experiment 1.

Males

Experimental Condition of Mothers				Organ Weight/Body Weight (mg/gm B.W.)				
Precon-ception	Ges-tation	Lac-tation	No. of Animals	Testes	Kidneys	Heart	Adrenals	Thyroids
.....	.....	.....	6	6.33	9.88	4.29	.35	.19
PTU	.....	.....	6	6.53	11.14	4.49	.30	.14
PTU	.....	PTU	5	4.72	11.32	4.57	.35	.58
PTU	PTU	.....	6	5.54	9.58	4.25	.36	.22
PTU	PTU	PTU	7	4.09	9.51	4.20	.34	.51

Females

				Ovaries	Kidneys	Heart	Adrenals	Thyroids
.....	.....	.....	6	.27	10.72	4.13	.26	.16
PTU	.....	.....	6	.35	10 87	4.63	.29	.16
PTU	.....	PTU	7	.38	10.63	4.32	.32	.61
PTU	PTU	.....	6	.28	10.45	4.71	.36	.22
PTU	PTU	PTU	5	.31	10.75	4.33	.36	.51

Table 5. Mammary-Gland to Body-Weight Ratios (gm/100 gm B.W.) of Some Mothers from Experiment I.

Experimental Condition				
Precon-ception	Ges-tation	Lac-tation	No. of Animals	Mammary-Gland to Body Weight Ratios (gm/100 gm B.W.)
....	....	....	4	5.06
PTU	....	....	4	6.28
PTU	....	PTU	4	5.37
PTU	PTU	....	4	5.27
PTU	PTU	PTU	4	6.14

Table 5 illustrates the mammary-gland to body-weight ratio of mothers of the five different groups. No trend was noticed in this measurement.

Experiment II

Table 6 shows the effect of continuous PTU treatment during the preimpregnation and gestation periods of female rats on the thyroid weight of their young. As noted, feeding of the drug during these periods results in an enlarged thyroid.

Table 6. Thyroid-Weight to Body-Weight Ratios (mg/gm B.W.) of Young of Experiment II at 24 Hours.

Experimental Conditon of Mother			
Precon-ception	Ges-tation	No. of[1] Animals	Thyroid-Weight to Body-Weight Ratio (mg/gm B.W.) of Young at 24 Hours
....	....	5	.25
PTU	PTU	6	.44

[1] No sex determination.

Table 7 illustrates the results of switching the young of normal diet females with the young of PTU-treated females at parturition. Survival rates, average litter weights, and thyroid-weight to body-weight ratios are presented.

Table 7. Foster Mother Data of Experiment II.

Experimental Condition of Natural Mother							
Precon-ception	Ges-tation	No. of Mothers in Group	Average Litter Size	Average[1] B.W. (gms)	Experimental Condition of Foster Mothers	Average B.W. (gm) at 3 weeks	Thyroid/B.W. Ratio (mg/gm) at 3 weeks
....	....	2	9.0	6.3	PTU	29.0[2]	.61
PTU	PTU	2	5.0	6.4		46.7	.23

[1] Switched to foster mother within 48 hours after birth.
[2] Cretins

Thus the propylthiouracil treatment, if continuous throughout preimpregnation and gestation, results in lower litter size as noted in this and in the previous experiment; and in enlarged thyroids, as noted in this experiment. If the young of PTU-treated females are removed from the source of their PTU supply, namely, their mothers and are nursed by foster mothers of a normal diet, they progress normally and their thryroid glands become smaller. On the other hand, young from normal-diet mothers suffer adverse effects when nursed by PTU-treated females. A cretin-like condition and enlarged thyroids result.

Experiment III

Table 8 compares the effects of PTU treatment during gesta-

tion periods, or lactation periods, or both, with normal diet during these times. All animals were fed normal chow during their preimpregnation period as noted previously.

Table 8. Comparison of PTU Treatment During Gestation and/or Lactation Periods with Normal Rats.

Preconception	Treatment During Gestation	Lactation	No. of Females in Gronps	No. of females successfully mated	Average No of Rats/Litter	Average No. of Rats/Litter at 24 Hours	Average B.W. of Rats at 24 hrs/gms
....	....	....	7	7	8.1	8.0	6.6
....	....	PTU	8	8	9.9	9.2	6.5
....	PTU	....	7	7	8.0	7.0	6.6
....	PTU	PTU	7	7	8.6	8.1	6.8

Whereas continuous treatment with PTU during preimpregnation and gestation in Experiment I resulted in low litter sizes, PTU treatment during gestation alone in Experiment III did not affect the litter size significantly. The weighted average litter size of the two groups on normal diet for gestation is 9.1 as compared to 8.3 for animals given PTU during gestation. However, it should be noted that one of the groups on PTU during gestation had a higher average litter size than one of those on normal diet.

In Table 9, the average body weights of offspring of the four groups measured at 24-hour and at weekly intervals are tabulated. As in the results for Experiment I, PTU treatment during gestation followed by a normal chow lactation period had but a slight effect on body growth whereas PTU treatment of mothers during lactation, regardless of prior treatment, resulted in cretin-like young. As contrasted to Experiment I, however, these cretins when weaned from their mothers had a 35% survival rate even if continued on PTU. At the end of five weeks of life, these animals weighed less than one-third than the controls.

Table 9. Average Weights of Young Resulting from Normal Rats and PTU Treatment During Gestation and/or Lactation; % Survival at Three Weeks.

Preconception	Treatment During Gestation	Lactation	at 24 Hours	1st Week	2nd Week	3rd Week	% Survival at 3 Weeks[1]
....	....	....	6.6	15.8	37.6	61.3	89
....	....	PTU	6.5	14.0	25.4	33.7°	80
....	PTU	....	6.6	14.5	30.7	50.5	82
....	PTU	PTU	6.8	12.1	18.9	24.8°	95

Preconception	Treatment During Gestation	Lactation	%Survival[2,3] at 5 Weeks	Average B.W. at 5 Weeks
....	....	....	100	99.3
....	....	PTU	40	35.0
....	PTU	....	100	98.2
....	PTU	PTU	30	29.0

° Cretins
[1] Compared to average no. rats/litter at 24 hours.
[2] Continued on same diet as mothers after weaning.
[3] Compared to Average no. rats/litter at 3 weeks.

Table 10 shows the organ-weight to body-weight ratios of representative young from each of the four groups. Results are

in good agreement with those of Experiment I, especially in respect to thyroid and testes weights. Again lactating mothers given PTU had young with enlarged thyroids and smaller testes. PTU treatment during lactation appeared to cause larger ovaries. Kidneys, heart, and adrenals were not affected.

Table 11 illustrates the mammary-gland to body-weight ratio of mothers of the four different groups. The mothers who had been treated with PTU during lactation had the highest ratios.

Table 10. Organ-Weight to Body-Weight Ratios (mg/gm body weight) of Some Young of Experiment III.

Experimental Condition of Mothers			Males					
				Organ- Weight/Body Weight (mg/gm B.W.)				
Preconception	Gestation	Lactation	No. of Animals	Testes	Kidneys	Heart	Adrenals	Thyroids
....	....	....	5	6.58	9.99	4.21	.36	.20
....	....	PTU	5	4.26	8.17	4.47	.32	.77
....	PTU	....	5	6.22	10.87	4.37	.35	.24
....	PTU	PTU	5	4.30	10.16	5.24	.41	.53
			Females					
				Ovaries	Kidneys	Heart	Adrenals	Thyroids
....	....	....	5	.28	10.62	4.03	.27	.15
....	....	PTU	5	.38	10.61	4.14	.36	.68
....	PTU	....	5	.29	10.12	4.29	.34	.26
....	PTU	PTU	5	.37	10.87	4.93	.41	.55

Table 11. Mammary-Gland to Body-Weight Ratios (gm/100gm B. W.) of Some Mothers from Experiment III

Experimental Condition				
Preconception	Gestation	Lactation	No. of Animals	Mammary-Gland to Body-Weight Rates (gm/100gm B. W.)
....	....	....	4	5.1
....	....	PTU	4	5.56
....	PTU	....	4	4.81
....	PTU	PTU	4	6.3

Table 12 shows the thyroid-weight to body-weight ratio of representative young from each of the four groups of Experiment IV. As noted, treatment with PTU during gestation resulted in a goitrous condition of the thyroid gland.

Table 12. Thyroid-Weight to Body-Weight Ratio (gm/gm body weight) of Some Young of Experiment IV at 24 Hours

Experimental Condition of Mother			
Preconception	Gestation	No. of Animals[1]	Thyroid-Weight to Body-Weight Ratio (mg/gm B.W.) of Young at 24 Hours
....	....	6	.21
PTU	....	6	.22
....	PTU	6	.42
PTU	PTU	6	.47

[1] No sex determination

Discussion

In spite of lowered metabolic rate and retardation of weight increase, no adverse effects on reproduction were observed in young female rats when the anti-thyroid drug, propylthiouracil, was administered up to the time of impregnation except in the sense that a slightly smaller litter size resulted. Within the first three experiments of this study, a total of 22 animals on normal

diet prior to impregnation produced an average litter size of 9.1, whereas, a total of 14 animals treated with PTU up to the time of impregnation but not after had an average litter size of 8.0. PTU treatment had not shown a disturbing effect on the length or regularity of the estrus cycle in the previous study reported (Cook, 1960). In a study with adult female guinea pigs, Peterson et al (1952) reported that cyclic activity as indicated by the frequency of vaginal openings in animals treated with 0.1% PTU for seven months, was not significantly affected and further, no sterile animals resulted from the treatment. The lack of effect of PTU on the length and regularity of the estrus cycle constrasts with those observed for the anti-thyroid drug, thiouracil, by Mann (1945), who demonstrated that 0.1% thiouracil resulted in the disruption of rhythmic pattern of activity with an increase in the length of periods between cornifications of vaginal mucosa. Barker (1949) reported a marked reduction in fertility in adult female rats which were fed 0.2% thiouracil for ten weeks. This was explained on the basis of disruption of the estrus cycle. It has been reported that in many species reproduction occurs despite thyroidectomy but the fecundity may be below normal (Peterson et al., 1952).

Continuous administration of PTU during preimpregnation and gestation resulted in some stillborn litters and lowered the number of offspring per litter when compared to PTU treatment during the preimpregnation period only (Table 2), but failed to influence the number of offspring significantly if given during gestation but not before conception (Table 8). Krohn and White (1949) demonstrated that the average number of young per litter was lowered by feeding thiouracil for 50 days to adult female rats with known breeding records. Leathem (1959) reported 0.5% thiouracil resulted in subnormal average litter sizes. Barrnett (1950) sacrificed young from cretin-like litters of female albino rats which were fed varying concentrations of thiouracil in their diet from the day of conception, and found that the thyroid glands of treated new-born animals showed hyperplastic changes. He attributed this to placental transmission of the thiouracil. Propylthiouracil-induced hypothyroidism was without detectable effect on reproductive performance in guinea pigs except that large goiters were present in the young born to such females (Peterson et al., 1952). The development of the goiters was attributed to the placental passage of propylthiouracil (Peterson and Young, 1952). It seems likely that PTU-placental transfer does take place in rats also and interferes with the continuation of development of embryos when administered both before and after conception. Since PTU does not seem to affect fertility in rats and the cessation

of its administration at conception eliminated the possibility of placental transfer, embryos develop normally. The lack of effect on litter size of PTU treatment initiated at conception may be due to the fact that the time required for clearance from the mother of thyroid hormone is long enough to allow successful implantation and early development of embryos. PTU-placental transfer during gestation does, however, interfere with the normal production of thyroxin by the young and a goitrous condition develops (Tables 6 and 12).

Propylthiouracil treatment of mothers during lactation resulted in a cretin-like condition with enlarged thyroid glands regardless of whether the drug was given to mothers before nursing or not (Tables 3, 4, 9, 10). The young rats did not have access to the PTU diet at any time during their nursing period. Barnett (1950) reported that the cretin-like litters from female rats fed varying concentrations of thiouracil in their diet from the day of impregnation showed a degree of retardation in growth and development in direct proportion to the dose of thiouracil used. He attributed the retardation to mammary transmission of the thiouracil. The present study did not utilize different dosages of PTU but it appears that PTU transfer in milk was the causative factor of cretin-like growth. Animals born under the same experimental conditions as those in Table 6, which had enlarged thyroid glands at 24 hours of age and presumably at parturition, did not have enlarged thyroid glands at weaning (Table 4) nor did they develop into cretins (Table 3) if their mothers were on normal chow during lactation. On the other hand, young with normal-size thyroid glands at birth developed into cretins and had goiters at weaning if their mothers were treated with PTU during lactation (Tables 3, 4, 6, 7, 9, 10). An analysis of the thyroid organ-weight to body-weight ratios (Tables 4, 10) reveals approximately the same degree of enlargement of the thyroid gland as reported for adult male and female rats treated with PTU.

Attempts were made several times to obtain milk samples from rats just prior to nursing of their young but were not successful. Thus no qualitative or quantitative data of milk samples are presented. The only significant points noticed in mammary-gland to body-weight ratios were that exposure to PTU at some time resulted in an increased ratio (Table 5) and PTU during lactation resulted in the highest ratios (Table 11).

A further analysis of the organ-weight to body-weight data reveals the typical picture of underdevelopment of the testes in cretinism (Leathem, 1959). It is interesting that in extremely young animals PTU decreases the testes to body-weight ratio,

whereas in older animals the PTU hypothyroidism increases the testes to body-weight ratio (Fregly and Hood, 1959). Similar results have been reported for thyroidectomized rats (Hess, 1953); hence, the increased testicular size is apparently the result of hypothyroidism induced by these two treatments. The testicular enlargement was described as true tissue hypertrophy and not due to water accumulation (Fregly and Hood, 1959). The ultimate cause and significance of the testicular enlargement is unknown. At any rate previous study would suggest that the enlarged testes of PTU-treated rats cannot be associated with impotence (Cook, 1960).

In summary, it would appear that although propylthiouracil administration to female rats does not affect fertility, it does affect litter size if treatment is continuous during preconception and gestation and has extremely adverse effects on young if given during the lactation period. The ill effects of the drug are attributed to placenta and milk transfer.

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