

1965

## The Influence of the Antithyroid Drug, Tapazole, on Reproduction in Rats

Daniel T. Geittmann  
*Coe College*

Copyright © Copyright 1965 by the Iowa Academy of Science, Inc.  
Follow this and additional works at: <http://scholarworks.uni.edu/pias>

---

### Recommended Citation

Geittmann, Daniel T. (1965) "The Influence of the Antithyroid Drug, Tapazole, on Reproduction in Rats," *Proceedings of the Iowa Academy of Science*: Vol. 72: No. 1 , Article 66.  
Available at: <http://scholarworks.uni.edu/pias/vol72/iss1/66>

This Research is brought to you for free and open access by UNI ScholarWorks. It has been accepted for inclusion in Proceedings of the Iowa Academy of Science by an authorized editor of UNI ScholarWorks. For more information, please contact [scholarworks@uni.edu](mailto:scholarworks@uni.edu).

# The Influence of the Antithyroid Drug, Tapazole, on Reproduction in Rats

DANIEL T. GEITTMANN<sup>1</sup>

*Abstract.* The antithyroid drug, Tapazole (methamazole, or imidazole-2- thio, 1-methyl), when fed to female rats at the dietary level of 0.1% had a slight effect on the average number of young and weight per litter if administered during the preconception period. If given during the gestation period the results were harmful. Tapazole treatment of mothers during lactation resulted in lethargic cretin-like young, although survival rates during lactation and after weaning were good.

## INTRODUCTION

Apgar (1964) stated that the drug Tapazole had no fetal or neonatal effect when administered to human mothers during pregnancy. Bondy and Hallman (1951) said that Tapazole had proved to be toxic in a few cases. There appears to be some doubt concerning the toxic effects of this drug. For this reason the present study was undertaken to obtain more information on the effects of Tapazole administration during preconception, and the influence of its administration during gestation and lactation in rats. A previous study had indicated deleterious effects of the drug on rats (Cook, 1963). This particular experiment in its procedural form parallels two studies involving another antithyroid drug, propylthiouracil (Cook, 1960, 1962).

## METHODS

In this experiment 32 female rats of the Holtzmann strain, approximately 96 days old at the beginning of the experiment, were used. The animals were placed into four groups and caged in a thermoregulated room maintained at  $25 \pm 1^\circ$  C and illuminated from 8:00 AM to 5:00 PM daily.

One of the four groups consisted of ten females and was fed finely ground Purina Laboratory Meal throughout the experiment. These animals, the controls, were placed with normal male rats and upon evidence of sperm were weighed and placed in maternity cages.

The second group of ten females was fed for 14 days with 0.1% Tapazole mixed thoroughly in ground meal before any attempt

<sup>1</sup> Student, Biology Department, Coe College, Cedar Rapids, Iowa

was made to mate them. Five of these ten females were housed in activity cages two weeks before the Tapazole and also during Tapazole feeding. Their activity was recorded daily. Upon the fourteenth day, attempts were made to breed the ten animals and within four days eight females had evidence of sperm. These eight animals were weighed and placed in maternity cages where they were fed normal meal without Tapazole.

The third group of seven females was fed normal meal and placed with males until five conceived. Upon conception the females were weighed and placed in maternity cages where they were fed 0.1% Tapazole mixed thoroughly in the ground meal. These animals were fed 0.1% Tapazole only during their gestation period and upon birth of their young they were once again given normal meal without Tapazole. Also two female rats from the control group that already had normal litters were placed in this group. Thus there were seven animals in this group. All were weighed at conception.

The fourth group of five females was fed normal meal without Tapazole and they were mated, weighed, and placed in maternity cages. Upon delivery of their young this group was fed 0.1% Tapazole (mixed thoroughly in the ground meal) until the young were weaned at the age of 22 days.

As mentioned, all female rats were weighed at the time of conception. They were also weighed at the first and second weeks after conception. The rats were observed frequently to see if any noticeable signs of irregular behavior resulted when 0.1% Tapazole was administered. The average litter sizes were determined 24 hours after birth. Survival rates were noted and average weights of the litters were measured at the end of a 22 day lactation period. The litters were weaned at the end of the 22 day lactation period and the young were fed a normal diet without Tapazole. The litters were also weighed during the first and second week of separation from their mothers.

## RESULTS

The body weights of the different groups upon conception and during the first and second week after conception are shown in Figure 1. It was found that Tapazole had an effect on the body weight of the females. When fed Tapazole they gained weight at a low rate as compared to the weight gains of the control group. It was also observed that the females fed Tapazole prior to conception had a lower average body weight than those fed Tapazole after conception. Upon removal of Tapazole from the diet, a marked increase of body weight was evidenced as indicated in Figure 1 where the females were fed Tapazole at

different stages. Along with a low rate of weight gain Tapazole also rendered the females nervous and reserved.

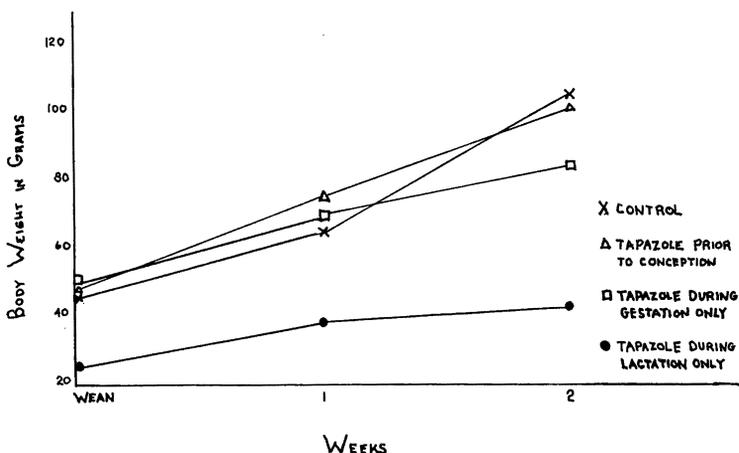


Figure 1. Effect of 0.1% Tapazole Diet on Body Weight Gain During the Gestation Period.

Tapazole was also found to have an effect on the length of the gestation period. The rats fed Tapazole during gestation only had a very lengthy gestation period as compared to the fairly long gestation period of those fed Tapazole two weeks prior to conception, and the relatively short gestation period of the control set as denoted by Figure 2.

Another interesting observation was the amount of activity by those rats fed a normal diet and then fed Tapazole two weeks prior to conception. As seen in Figure 3 the activity of the rats, while on a normal diet, was high and fairly uniform. As soon as they were placed on the 0.1% Tapazole diet their activity decreased and the uniformity of their peaks became very irregular.

Upon delivery of the young it was observed that Tapazole fed during gestation had an effect on the size of the litter and the number of stillborn. Two rats in this group produced stillborn young, and ate what few living young they had. The rats fed Tapazole two weeks prior to conception also had a small litter when compared to the litter size of the control group as shown in Table 1. Of all the females mated, about two females from each group did not deliver and had no visible signs of aborting any fetal material. One, fed Tapazole two weeks prior to conception, was found dead in her cage. An autopsy revealed an enlarged thyroid and a dark green skin surrounding her abdominal area. There was no fetus.

Another interesting observation was the comparison of weight gain between the litters of the female rats fed Tapazole two weeks prior to conception, during gestation, and lactation as compared with the control group. The weight checks on the litters were made on the twenty-second day of the lactation period and after the first and second weeks of weaning which

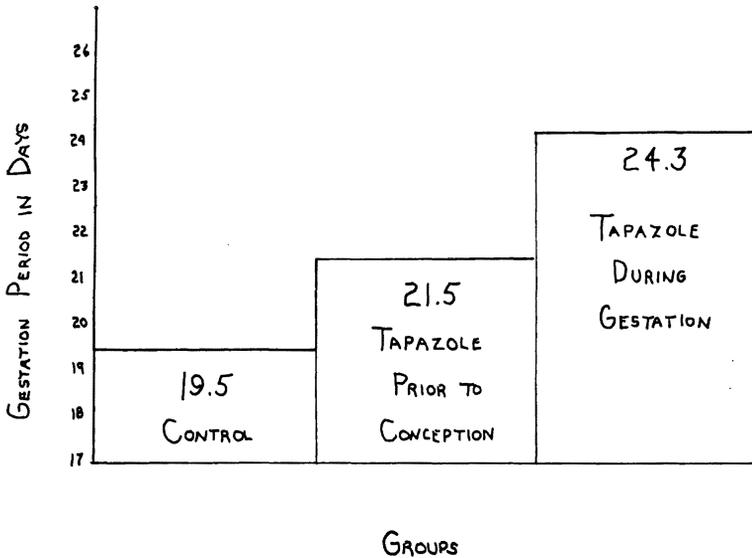


Figure 2. Graph of Average Gestation Period of Female Rats Fed 0.1% Tapazole Diet During Gestation, 2 weeks Prior to Conception, and a Control Group.

Table 1. Comparison of reproductive ability of normal rats and rats treated with tapazole during various periods.

	No. of Females in Group	No. of Females Who Successfully Delivered	Ave. No. Rats/Litter	Ave. No. Stillborn/Litter
Control	10	9	11.5	0.9
Fed Tapazole 2 weeks prior to conception	10	8	9.5	0.87
Fed Tapazole during gestation	7	4	7.7	3.0

occurred on the twenty-second day of the lactation period. The weight gain of the control group was relatively large and progressed at a uniform rate as compared to the low uneven gains of the group fed Tapazole, shown in Figure 4.

Even though Tapazole was administered only to the mothers, the litters of the gestation and lactation groups showed visible signs of cretinism and were lethargic for a period of time after birth. The group fed Tapazole during lactation had the most pronounced cretinism as evidenced by scaly tails and feet, beady

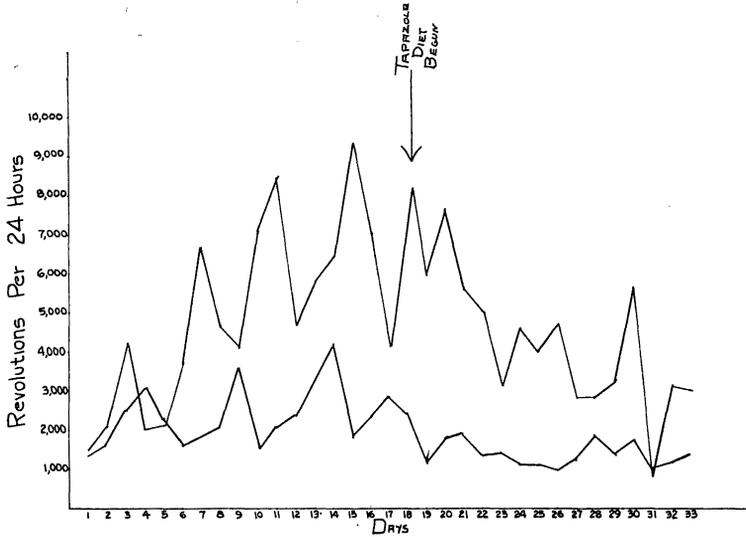


Figure 3. Graph of the activity of female rats two weeks before they were fed tapazole and two weeks while they were fed tapazole.

eyes, tiny ears, shaggy coats, and lethargic actions. These symptoms lasted until the mother was taken off Tapazole and placed on a normal diet. The female fed Tapazole during gesta-

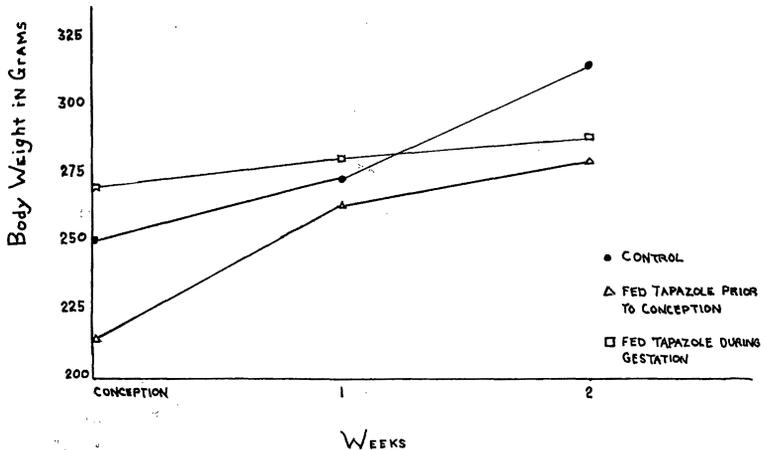


Figure 4. Average weights of young resulting from normal rats and tapazole-fed mothers.

tion had a small litter characterized by scaly bodies. This female was taken off Tapazole as soon as she gave birth and was then fed a normal diet. Her young developed slowly, lost their scales,

and took on a healthy appearance. The females fed Tapazole two weeks prior to conception delivered apparently normal litters, and the young grew at a normal healthy rate as compared to the growth rate of the control group.

#### DISCUSSION

The results of this experiment indicate that Tapazole definitely has an effect on gestation and lactation in female rats. It appears that Tapazole is not a long-range drug. When it was administered to female rats two weeks before conception, the young showed no visible effects. Their young in all respects of growth and litter size resembled the control group. On the other hand, Tapazole had a powerful short-range effect on the young of mothers fed Tapazole during gestation and lactation. This finding parallels that of the staff of New York Medical College who found Tapazole to be a high potent and rapidly acting drug on humans (Staff of New York Medical College, 1950). The results of the present experiment clearly showed that when Tapazole was administered to seven female rats after they had conceived, as denoted by vaginal smears, three females did not produce litters and no evidence of aborting. Two other females had a prolonged gestation period and litters consisting of four or more still born, and the few alive they ate. Only two females in this group had litters that lived. One had a long gestation period and a litter of eight characterized by cretinous growth and lethargy. The other female had a litter of ten, four of which were stillborn and the six, living, characterized by cretinous growth. As soon as their mother was taken off 0.1% Tapazole diet their appearance improved and their growth rate increased, implying that as soon as the Tapazole diet was terminated, regular growth at once occurred. The powerful short-range effect of Tapazole can be seen in the group fed Tapazole only during lactation. The mothers had normal-sized, healthy litters. Within one week the young started to appear scaly and stunted. After the second week the young had all the symptoms of cretinism and were very lethargic. At this stage the young were observed very closely and it was noted that they had no access to their mother's 0.1% Tapazole meal. This directly implies that the Tapazole transfer in milk was the cause of cretin-like growth as similarly seen in Barnett's work (1950) when he attributed the retardation to mammary transmission of thiouracil, another antithyroid drug.

In summary, Tapazole appears to have a powerful short-range effect on the female rat during gestation and lactation, because of its effect on gestation length, litter size, and litter growth. Although Tapazole appears to have harmful effects on litters,

removal of this drug from the rats' diet with replacement by a normal diet, results in rehabilitation within a matter of weeks, but it is not fully understood what degree of rehabilitation does occur.

When compared to the previously mentioned propylthiouracil, the effects of Tapazole during gestation are much more harmful than those of the former since propylthiouracil treatment during gestation alone did not affect the litter size significantly (Cook, 1963). This is in accord with the reported potency of the two drugs where Tapazole is said to be ten times as strong as propylthiouracil (Irwin et al 1952).

#### ACKNOWLEDGEMENT

I wish to acknowledge the aid of Dr. Kenneth M. Cook, Coe College, who suggested this study to me and who read over the manuscript.

#### Literature Cited

- Apgar, V. 1964. Drugs in Pregnancy. *J. Am. Med. Assoc.* 190:104-105.
- Barnett, R. J. 1950. The Experimental Production of Cretin-like Rats. *Yale J. Biol. Med.* 22:315-322.
- Bondy, P. K. and B. L. Hallman. 1951. Experience with Methimazole (Tapazole) in the Treatment of Hyperthyroidism. *Am. J. Med.* 11:724-729.
- Cook, K. M. 1960. The Influence of the Antithyroid Drug, Propylthiouracil, on Reproduction in Rats. *Iowa Acad. Sci.* 67:463-470.
- , 1962. The Influence of the Antithyroid Drug, Propylthiouracil, on Gestation and Lactation in Rats. *ibid.* 69:622-635.
- , 1963. Personal Communication.
- Irwin, G. W., M. S. Norris, and H. D. Van Vactor. 1952. Propylthiouracil and Methimazole Therapy. *J. Am. Med. Assoc.* 149:1637-1640.
- Staff of the New York Medical College. 1950. Antithyroid Compounds. *Am. Med. Assoc. Exhibit*, San Francisco.