control subjects. 2. The rate of serum protein formation thus determined would appear to be greater in the nephrotic patients than in the control subjects.

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Effects of Hypo- and Hyperthyroidism in Rats and Mice on Ovarian Response to Equine Gonadotrophin.* (18129)

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The effects of thiouracil and thyroprotein on the response of the testes and seminal vesicles of young rats and mice to a constant dose of pregnant mares' serum has recently been reported(1). It was found that thiouracil increased the gonadal response to PMS in rats but decreased it in mice. Thyroprotein decreased the gonadal response to PMS in rats but increased it in mice. Sex differences have been found in the normal thyroid secretion rate of male and female rats and mice(2,3). Other differences between the sexes may also modify the end-organ responses of animals to hormonal stimuli. It was considered of interest, therefore, to determine whether the gonadal response of female rats and mice to PMS would be altered in the same directions by thiouracil or thyroprotein as previously found in males of the two species.

Methods. Young female albino rats (Michigan State College strain) and mice (Rockland strain) were used in these experiments. The rats averaged 40 to 50 g in weight at the beginning and 80 to 100 g at the end of the experiments. The mice weighed 8 to 12 g at the beginning and 17 to 21 g at the end of each experiment. The animals were housed in an air-conditioned room with a mean temperature of 74°F. Hyperthyroidism was induced in the rats and mice by incorporating thyroprotein‡ in the ration in concentrations of 0.02 to 1.28%, and feeding for 10 days. In one series of rats hyperthyroidism was produced by injecting d, l-thyroxine subcutaneously for 10 days in doses equivalent to 1.5 to 12 times their approximate normal thyroid secretion rate. Hypothyroidism was induced in the rats and mice respectively by feeding 0.1% and 0.2% thiouracil. The degree of hypothyroidism was controlled by feeding the thiouracil for 4 to 20 day periods. The animals which were to receive thiouracil for the longer periods were started at lower body weights than the controls in order to reach approximately the same body weights at the end of each experiment.

During the last 4 days of each experimental period, the rats were each injected subcutaneously with a constant dose of one Cortland-Nelson unit (20 I.U.) of pregnant mares' serum ("Gonadogen")§ and each mouse with one half of this dose. On the day of autopsy, the ovaries were removed and weighed on a Roller-Smith balance. The weights of the ovaries were calculated on a 100 g body weight basis.

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1. Meites, J., and Chandrashaker, B., *Endocrinology*, 1949, v44, 368.

2. Monroe, R. A., and Turner, C. W., *Mo. Agr. Exp. Sta. Res. Bull.*, 1946, 403.

3. Hurst, V., and Turner, C. W., *Mo. Agr. Exp. Sta. Res. Bull.*, 1948, 417.

‡ Thyroprotein ("Protamone") was made available through the courtesy of Dr. W. R. Graham, Jr. of Cerophyl Labs, Inc., Kansas City, Mo.

§ Kindly supplied by Dr. J. Lavere Davidson, Department of Veterinary Medicine, The Upjohn Co., Kalamazoo, Mich.

TABLE I. Effects of Thyroxine, Thyroprotein, and Thiouracil on Ovarian Response to PMS in Rats and Mice.

Species	No. of animals	Treatment		Avg wt of ovaries, 100 g body wt
		Was PMS given?	Other	
Rat	6	No	None	25.2 ± 0.9*
"	6	Yes	"	99.0 ± 4.6
"	12	"	6.9- 9.2 γ thyroxine	71.5 ± 2.7- 69.6 ± 1.8
"	18	"	18.4-55.2 γ "	57.7 ± 0.8- 41.7 ± 1.3
"	11	"	.04-.08% thyroprotein	66.6 ± 1.5- 63.9 ± 1.2
"	23	"	.16-32% "	59.7 ± 1.4- 49.7 ± 1.7
"	12	"	4 days thiouracil	154.0 ± 3.1-161.8 ± 2.4
"	12	"	7 " "	183.3 ± 2.1-189.4 ± 2.6
"	16	"	10-15 days thiouracil	112.4 ± 1.7-104.7 ± 1.9
"	12	"	20 " "	65.3 ± 1.3- 66.2 ± 2.6
Mouse	14	No	None	27.8 ± 1.1
"	7	Yes	"	41.5 ± 1.3
"	14	"	.02-.04% thyroprotein	41.1 ± 1.3- 51.1 ± 1.5
"	14	"	.08-.16% "	52.3 ± 2.9- 55.7 ± 2.5

* Standard error of mean = $\sqrt{\frac{\Sigma d^2}{n(n-1)}}$

Results. The data are summarized in Table I. Many of the groups of rats and mice, which averaged 6 and 7 per group respectively, have been combined in the table whenever the trend of the results was in the same direction. In the rats the administration of PMS alone increased the average weight of the ovaries from 25.2 ± 0.9 to 99.0 ± 4.6 mg. Both thyroxine and thyroprotein drastically reduced the response of the ovaries to PMS. The largest doses of thyroxine or thyroprotein given reduced the ovarian response to PMS approximately by half when compared with the group receiving PMS alone.

Thiouracil greatly increased the response of the ovaries of the rats to PMS when given for 4, 7, 10 and 15 day periods. The 7 day treatment with thiouracil increased the weight of the ovaries to twice that elicited by PMS alone. When given for 20 days, thiouracil effected a significant reduction in ovarian response to PMS in 2 groups of rats. Apparently, an extreme degree of hypothyroidism in female rats is not favorable to gonadotrophic action on the ovaries.

In the mice the injection of PMS alone increased the average weight of the ovaries from 27.8 ± 1.1 to 41.5 ± 1.3 mg. Thyroprotein significantly increased the response of the ovaries to PMS, with the largest dose, 0.16%, producing the greatest increase. It will be noted that this effect of thyroprotein in the mice is just opposite to that obtained in the rats. Several groups of mice were treated with thiouracil, but the results were so inconclusive that they are not presented here.

Discussion. The results of these experiments in female rats and mice are in general agreement with the findings of Meites and Chandrashaker in male rats and mice(1). The one notable exception was that feeding thiouracil for 20 days reduced the action of the gonadotrophin in the female but not in the male rats. Feeding thiouracil for 4 to 15 days increased the gonadal response to PMS in rats of both sexes. It is believed that the possible effects of thiouracil or thyroprotein on the secretion of gonadotrophins by the animal's own pituitary can be eliminated as an important factor in these experiments. It was shown previously that these substances alone had no apparent effects on testes and seminal vesicle weights when given for 10 day periods to immature male rats and mice(1).

These data indicate that insofar as the gonadal response to PMS is concerned, young rats of both sexes secrete more than an optimal amount of thyroid hormone while young mice of both sexes secrete less than an optimal amount. These differences in thyroid status probably account for other anomalous

reactions to hormonal stimuli observed in the two species. Thus, thiouracil has been shown to decrease body growth(3) and mammary growth(4,5) in mice, but increase body growth(6) and mammary growth(5,7) in rats. Thyroid administration has been demonstrated to increase body growth(8) and mammary growth(9) in mice, but decrease body growth (8) in rats. It is not definitely known how thyroidal substances exert their modifying influences on the reaction of the gonads of rats and mice to PMS. A recent report by Warner and Meyer(10) indicates that in rats the administration of thyroxine probably acts directly on the ovaries to inhibit their reaction to endogenous gonadotrophins.

Summary. The effects of experimentally induced hypo- and hyperthyroidism on the ovarian response to pregnant mares' serum were determined in immature rats and mice by administering thiouracil for 4 to 20 days and thyroxine or thyroprotein for 10 days. A constant dose of PMS was injected into each animal during the last 4 days of each experiment and the increase in ovarian weight was measured. It was found in rats that all doses of thyroprotein or thyroxine significantly decreased the action of the gonadotrophin on the ovaries, while in mice thyroprotein significantly increased the ovarian response to PMS. When thiouracil was fed to rats for 4, 7, 10 and 15 day periods, there were significant increases in ovarian response to PMS, but when fed for 20 days thiouracil reduced the ovarian response to PMS. These data on young female rats and mice corroborate the results previously obtained in young male rats and mice. It is suggested that insofar as the ovarian response to PMS is concerned, young rats of both sexes secrete more and young mice less than an optimal amount of thyroid hormone.

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4. Mixner, J. P., *J. Dairy Science,* 1947, v30, 578.
5. Trentin, J. J., Hurst, V., and Turner, C. W., PROC. SOC. EXP. BIOL AND MED., 1948, v67, 461.
6. Astwood, E. B., The Harvey Lectures, N. Y. Acad. of Med., Science Press Printing Co., Lancaster, Pa., 1945.
7. Johnston, R. F., and Smithcors, F., *Endocrinology,* 1948, v43, 193.
8. Koger, M., and Turner, C. W., *Mo. Agr. Exp. Sta. Res. Bull.,* 1943, 377.
9. Mixner, J. P., and Turner, C. W., *Mo. Agr. Exp. Sta. Res. Bull.,* 1943, 378.
10. Warner, E. D., and Meyer, R. K., *Endocrinology,* 1940, v45, 33.

Effect of 5-Amino-7-Hydroxy-1H-v-Triazolo (d) Pyrimidine on Growth and Development of the Chick Embryo.* (18130)

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In 1949, Kidder and his associates(1) reported that the growth of the protozoan, *Tetrahymena gelii,* and certain mammalian tumors was inhibited by the guanine analogue, 5-amino-7-hydroxy-1H-v-triazolo (d) pyrimidine (guanazolo).† Other investigators have studied the effect of this agent on a wider range of neoplasms and considerable variation has been observed in the response of different tumors to it(2-4).

The purpose of this communication is to

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1. Kidder, G. W., Dewey, V. C., Parks, R. E., Jr., and Woodside, G. L., *Science,* 1949, v109, 511.

† The alternate designation, "8-azaguanine", has been suggested for this compound(3).

2. Gellhorn, A., Engelman, M., Shapiro, D., Graff, S., and Gillespie, H., *Cancer Res.,* 1950, v10, 170.
3. Sugiura, K., Hitchings, G. H., Cavalieri, L. F., and Stock, C. C., *Cancer Res.,* 1950, v10, 178.
4. Law, L. W., *Cancer Res.,* 1950, v10, 186.