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Age and the Qualitative Ovarian Response of the Immature Rat to Mare Gonadotropic Hormone.

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It was shown[1] that 21- and 25-day-old rats responded to mare gonadotropic hormone with follicular growth, ovulation, and the formation of corpora lutea. Later it was shown[2] that in female rats 10 days old at the time of the injection the response consisted in a marked development of interstitial tissue. This divergence in results led us to study further the nature of the response dependent upon age.

Rats were divided into groups with age and size of the dose as the variables. Single doses of 2, 16, and 500 R. U. were given to rats 15, 18, 19, 21, and 25 days old at the time of injection with necropsy 120 hours after the injection. The ovaries and uteri were weighed and the ovaries of three rats in each group were sectioned serially. The response of the 15-day-old rats is comparable to that of 10-day-old rats and thus does not need further consideration.

A pure follicle stimulating response was obtained at all dosage levels with rats injected on the 18th day. Not a single corpus luteum was found in 26 rats injected at this age. Macroscopically enlarged pale translucent follicles were visible. Microscopic study shows that ovulation has not occurred and there is no evidence of the conversion of the granulosa into lutein tissue. There is, however, a marked development of interstitial tissue in rats receiving the larger amounts, which is in many ways similar to that found in the ovary of the rabbit in heat. In those receiving 2 R. U. the only detectable change is the growth of a few follicles.

Ovulation and the formation of corpora occurred in 3 of 18 rats injected on the 19th day of age, and the results in 21- and 25-day-old rats were comparable to those previously obtained.

The question arises as to why this difference in response dependent upon age is obtained. One might assume that a luteinizing substance is secreted by the pituitary in the 25- but not in the 18-day-old rat, thereby accounting for luteinization in the older rat. Casida[3] obtained some results in favor of this view. He injected extracts of

[1] Cole, H. H., Guilbert, H. R., and Goss, H., *Am. J. Physiol.*, 1932, **102**, 227.

[2] Cole, H. H., *Am. J. Anat.*, in press.

[3] Casida, L. E., *Endocrinology*, 1934, **18**, 714.

gelding pituitaries into 2 strains of rats. In one a pure follicle stimulating response was noted whereas in the other ovulation occurred with the consequent formation of corpora lutea. When a small amount of pituitary luteinizer was added to the gelding pituitary extract and injected into the first mentioned strain ovulation occurred. Against such a view, however, is the fact that Smith[4] was able to produce both follicular growth and luteinization in hypophysectomized rats with mare gonadotropic hormone. This, it seems, should be conclusive proof that luteinization following mare gonadotropic hormone treatment is not dependent upon a factor secreted by the pituitary of the recipient. If this is true, then the difference in response must be explained either on the basis of the state of the ovary at the moment of injection or by assuming that a second factor is secreted elsewhere in the body.

The results given in this paper point out clearly the necessity of knowing the stage of sexual development of rats used in studying the qualitative response to gonadotropic substances. As different strains of rats mature at different ages it is obvious that different responses might be obtained in 2 strains of rats even though their ages were the same. This may to some extent explain the divergent results obtained with pituitary extracts in different laboratories.

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Means of Augmenting the Ovarian Response to Gonadotropic Substances.

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We presented evidence[1] that the serum of the pregnant mare contains 2 substances, one which produces sexual maturity and fully formed corpora lutea in the immature rat and another which is ineffective by itself but is capable of augmenting the response to pituitary synergist prepared after the method of Evans, *et al.*[2] We obtained augmentation of this synergist by the use of a fraction prepared from mare serum after the method described by Fevold

[4] Smith, P. E., *J. Am. Med. Assn.*, 1935, **104**, 553.

[1] Saunders, F. J., and Cole, H. H., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1476.

[2] Evans, H. M., Simpson, M. E., and Austin, P. R., *J. Exp. Med.*, 1933, **58**, 545.