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# Neurobiology of Reproduction in the Female Rat

A Fifty-Year Perspective

With 73 Illustrations



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To Marian

## Preface

It has been my privilege and pleasure during the past half century to participate in the unfolding of present-day concepts of the mammalian female reproductive cycles. When the studies recorded here began in the late 1930s it was already established that cyclic ovarian function is governed by gonadotropic secretions from the anterior pituitary gland, the "conductor of the endocrine orchestra," and that in turn this activity is importantly dependent in some way upon secretion of estrogens and progesterone by the ovaries. Although a role of the nervous system was recognized for the reflex-like induction of ovulation in rabbits and cats and the induction of pseudopregnancy in rats and mice, and although there was even some evidence of neural participation in ovulation in rats, a major central neural role in the female cycle of most species was not apparent. Gonadotropic fractions of pituitary extracts having distinct follicle-stimulating and luteinizing activities in test animals had been obtained, and these respective effects had been fairly well characterized. Prolactin was well known for its lactogenic activity, but its luteotropic role in rats and mice had yet to be revealed. The molecular structure of the several estrogens and progesterone was known, and they were readily available as synthetic products. The broad concept of ovarian-pituitary reciprocity appeared to be an acceptable explanation of the female cycle, with the ovary in control through the rhythmic rise and fall in secretion of follicular estrogen. George Corner in his book *The Hormones in Human Reproduction* (Princeton University Press, 1942) would include a chapter entitled *The Ovary as Timepiece*.

There were known to be modifying influences of the environment on reproduction, however, which in themselves implied some participation of the nervous system; seasonal changes were obvious in many species. In rats, it was known that exposure of cycling females to continuous illumination would induce a persistent state of vaginal cornification, failure of ovulation and the presence of polyfollicular ovaries lacking corpora lutea. The existence of a "sex center" in the rat hypothalamus had been proposed, and the importance of the pituitary stalk for ovulation had been demonstrated in both rabbits and rats. However, the special importance of the hypophysial portal vasculature for anterior pituitary regulation was speculative at best.

It was fortuitous that after coming to Duke University, for continuing my studies of the rat placenta I felt it necessary to use animals of the same stock that I had used in New Haven; I chose to use close inbreeding by brother-sister matings. Probably as the result of the mixed heredity of the breeding stock the inbreeding

soon brought out the tendency toward the occurrence of spontaneous persistent vaginal estrus in the early life of nonbreeding females and toward a special sensitivity to environmental illumination. These striking features begged for investigation, diverted me from the placenta and led to the long series of investigations that are the subject matter of this monograph.

August, 1989

John W. Everett

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