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This Week's Citation Classic

Lisk R D. Estrogen-sensitive centers in the hypothalamus of the rat.
J. Exp. Zool. **145**:197-207, 1960.
[Dept. Biology, Harvard Univ., Cambridge, MA]

The findings demonstrate that estrogen implantation at specific brain sites (medial basal hypothalamus) blocks gamete maturation in the gonads and results in atrophy of the reproductive tract. Thus, regulation of gonadotrophin secretion from the pituitary is via hormone sensitive neural mechanisms located within the medial basal hypothalamus. [The *Science Citation Index*® (*SCI*®) and the *Social Sciences Citation Index*® (*SSCI*®) indicate that this paper has been cited over 175 times since 1961.]

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"This paper was part of my PhD dissertation based on studies carried out in the biological laboratories at Harvard University. During summers, while an undergraduate, I worked as a field assistant at the L. Opinicon Field Station of Queen's University, Kingston, Ontario. I was responsible for collecting data for a study of population dynamics in the white-footed mouse. This sparked an interest in reproductive biology which developed into my lifework. I quickly became convinced that one had to work in the laboratory to gain a deeper insight of how reproduction was regulated. First, I searched the literature to identify 'leaders' in reproductive biology. The name of Frederick Hisaw kept popping up and he appeared to be a 'father figure' in the field.[1] I was interested not just in the physiology of reproduction but also in the behavioral changes necessary for mating to occur. Hisaw was at Harvard as was Donald Griffin, who was doing exciting behavioral studies on bats' discrimination ability.[2]

"I was accepted at Harvard and prepared a literature review which demonstrated that destruction of a specific brain site could block the ovulatory cycle while lesioning of a separate site blocked the display of mating behavior without interfering with the ovulatory cycle. Therefore, I argued that the steroid hormones made in the ovaries must feed back onto specific sites in the brain to regulate the ovulatory cycle as well as facilitate mating behavior. My mentors, particularly Griffin, were convinced that I had something and asked what I needed to test this hypothesis. I replied that I needed a stereotaxic apparatus so that I could implant the steroid hormones at specific sites in the brain. In a few weeks a wooden box arrived; I opened it and there was a stereotaxic apparatus. All I had to do was learn how to use it and decide how I would secure the hormone at the brain sites of interest. This was solved by carefully melting the crystalline hormone and drawing it up by capillary action into stainless steel tubing. The tubing was lowered into the brain through a hole drilled in the skull and the tubing cemented in place with dental acrylic. The findings are summarized above.

"This study provided the first direct evidence that a gonadal hormone could act at the brain to regulate physiology. Such a radical conclusion was too giant a leap for the establishment. Thus, my paper was turned down by *Endocrinology* and came to be published in the *Journal of Experimental Zoology*. This paper has been highly cited for the following reason. Even though the findings appeared in a journal less likely to be scanned by physiologists and psychologists, the power of the technique for mapping hormone-sensitive brain areas in relation to their function was recognized.[3] Today many laboratories employ this technique to study hormone feedback control of physiology and behavior and the findings appear in the major journals both in biology and psychology."

1. **Hisaw F L & Astwood E B.** The physiology of reproduction. *Annu. Rev. Physiol.* 4:503-60, 1942.
2. **Griffin D R.** *Listening in the dark: the acoustic orientation of bats and men.* New Haven, CT: Yale University Press, 1958. 413 p.
3. **Lisk R D & Barfield M A.** Sites and mechanisms of steroid effects on behavior. (Stumpf W A & Grant L D, eds.) *Anatomical neuroendocrinology.* Basel: S. Karger, 1975. p. 232-44.