

Classic illustrations ...

## J.E. Markee: Menstruation in intraocular endometrial transplants in the rhesus monkey

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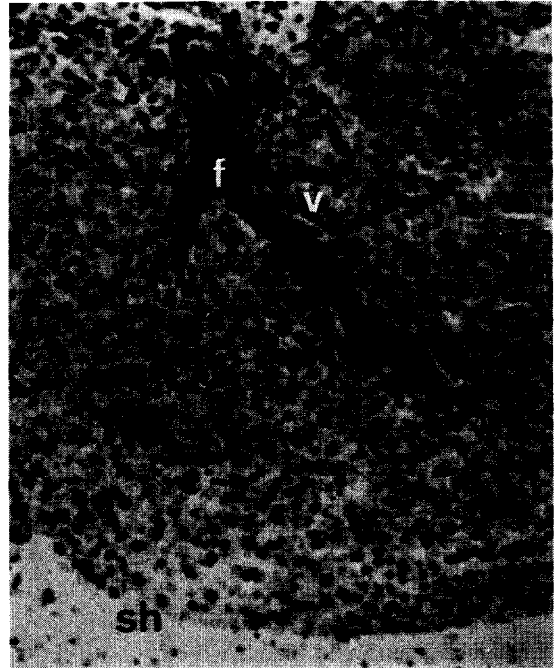
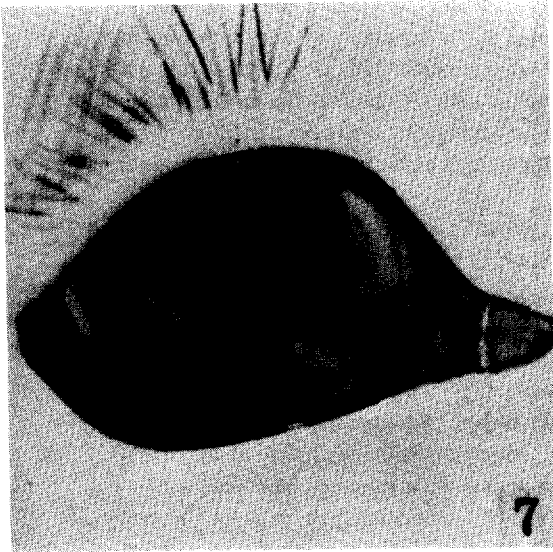


Fig. 1. Photograph of an endometrial transplant in the anterior eye chamber of a Rhesus monkey. Bleeding has begun from a previously formed hematoma. A few minutes after the photograph was taken, the eye was full of blood. The animal was held on its side while being photographed. Figure taken from: Markee, J.E. (1940): Menstruation in intraocular endometrial transplants in the rhesus monkey. *Contr. Embryol. Carneg. Inst.*, 28, pp. 219–308.

Fig. 2. Light micrograph of a paraffin section of an uterus extirpated 7 hours after the onset of clinical menstrual bleeding. An endometrial vessel (v) ending on the shedding surface (sh) is occluded by fibrin (f);  $\times 260$ . Figure taken from: Sixma, J.J., Christiaens, G.C.M.L. and Haspels, A.A. (1980): The sequence of haemostatic events in the endometrium during normal menstruation. In: *Endometrium Bleeding and Steroidal Contraception*. Editors: Diczfalusy, Frazer and Webb. Pitman Press, Bath, England.

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Whenever menstruation is discussed, the classic work of Markee on endometrial transplants in Rhesus monkeys is mentioned (Markee, 1940). Even before Markee's experiments, histological studies of menstruating uteri had been performed in primates (Van Herwerden, 1905) and humans (Bartelmez, 1933), but the experimental design of Markee was totally new.

To make the uterine mucosa accessible to the investigators' eye, Markee transplanted endometrium into an *in vivo* observation chamber, the anterior eye chamber of Rhesus monkeys (Fig. 1). In this way he was able to observe the events during 432 cycles, especially during menstruation, a work that took him about 9 years. The results were clearly described in an 89 page article (Markee, 1940) and resumed in several shorter papers (Markee, 1948, 1950).

The most important data from the original work of Markee are the following.

Menstruation appeared always to be preceded by a period of rapid regression with a decrease in height of up to 75% of the endometrium. This phenomenon is now known to all pathologists. Additional experiments with exogenous hormones proved that this regression is caused by local hormone withdrawal. Markee attributed a role to the regression in the causation of menstruation, and stated that regression is more important for tissue shrinkage than shedding.

Four to 24 hours before the onset of menstruation, the endometrial transplant (and not the receptor eye) suffered from a period of prolonged vasoconstriction. Markee ascribed the vasoconstriction to an unknown vasoconstrictor substance. Recent work has shown that intravenous administration of the vasoconstrictor  $\text{PGF}_{2\alpha}$  during the luteal phase (Turksoy and Safaii, 1975) or after a missed menstrual period (Wentz and Seegar Jones, 1973) is capable of inducing tissue breakdown and menstruation. In agreement with this, the concentration of  $\text{PGF}_{2\alpha}$  is elevated in the late secretory and menstrual endometrium (Willman et al., 1976). Hence,  $\text{PGF}_{2\alpha}$  could be the unknown vasoconstrictor substance of Markee.

Menstrual bleeding appeared to start when the endometrium was sufficiently damaged by stasis to degenerate, and is due to periodic relaxation of the vessels. Vasoconstriction in the spiral arteries persists throughout menstruation and then safeguards against excessive blood loss. Recent studies have shown that hemostasis is also attained through the formation of 'hemostatic thrombi' (Christiaens et al., 1980) (Fig. 2). Markee observed such occlusive intravascular material, but did not recognize it as platelet/fibrin thrombi due to the use of low magnification and the absence of specific staining.

The transplants used by Markee were free of myometrium and hence the myometrium seemed not essential to premenstrual regression and menstrual desquamation.

The uniqueness of Markee's work resides in his experimental design which enabled him to define precisely the onset of menstruation. Up to now all other morphological studies of menstruation have had to rely on the beginning of clinical bleeding which may be inaccurate since we do not know how long menstrual discharge is retained in the uterus before it is expelled toward the vagina. The patience and time required for Markee's experiments must have been tremendous and attempts to reproduce them have been unsuccessful hitherto (Beller and Schweppe, 1979). Many observations and descriptions of Markee are still valid now,

and the precise diary of a 3-day observation period, added to the manuscript, is still worth reading.

## References

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