This work was supported by the Swedish Medical Research Council (04X-502). Leo, Helsingborg and Endo Laboratories, Garden City, N.Y. generously donated drugs. We are grateful to Maria Lindbäck for excellent technical assistance.

July 21, 1978

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Inhibition of oestrogen-induced increase in uterine blood flow in the rat

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Studies in the ovariectomized rat have shown that uterine blood flow may be significantly increased by treatment with oestrogen (Spaziani & Suddick, 1967). This response may be modified by pretreatment with mepyramine (a histamine H_1-receptor antagonist), cellulose sulphate (a kininogen depleting agent) and inhibitors of prostaglandin synthesis. However, pretreatment with any of these pharmacological agents never produced more than a 50% inhibition of the oestrogen-induced response (Phaily & Senior, 1978). It appears that the mediators may be acting synergistically to increase the uterine blood flow and this experiment was designed to test the hypothesis.

The methodology and validation of the measurement of uterine blood flow using a labelled microsphere technique have been previously reported (Phaily & Senior, 1978). Mature virgin female rats were used (200–250 g) housed in light and temperature controlled conditions. The rats were bilaterally ovariectomized by the dorsal route at least 14 days before the experiments were made. Oestradiol (oestra-1,3,5(10)-triene-3,17-diol) (BDH, Poole, U.K.) was administered in a 10% (v/v) solution of propylene glycol into the tail vein of the restrained rat 1 h before the blood flow determinations were made. Pretreatment, where used, was as follows: A prostaglandin synthesis inhibitor, AH 7170 (2-*m*-(*p*-chlorobenzoyl) phenyl-propionic acid) (Allen & Hanbury Research Ltd., Ware, U.K.) was dissolved in 10% (w/v) sodium bicarbonate solution and administered orally in a dose of 1 mg kg^{-1} twice daily for two days, the last dose was given 60 min before oestradiol was injected. Cellulose sulphate, prepared by the method of Astrup, Galsmar & Volkert (1944), was given at 1 mg kg^{-1} (i.v.) into the restrained rat, mepyramine maleate (May & Baker, Dagenham, U.K.), was given at 5 mg kg^{-1} (i.p.); both drugs were dissolved in 0·9% (w/v) NaCl and given 60 min before the oestradiol injection.

The results were analysed using Student's *t*-test modified to compare samples having different variances (Snedecor & Cochran, 1967).

Blood flow through the uterus in the ovariectomized rat is low and only represents around 0·07% of the total cardiac output (Table 1). This result is at the lower limit of the estimation procedure. Injection of oestradiol produces an increase in uterine blood flow 1 h after the injection but the rise is almost completely inhibited by

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Table 1. *The effect (mean ± s.e.m.) of pretreatment with mepyramine maleate, cellulose sulphate and AH 7170 on the uterine blood flow at 60 min after intravenous injection of 0·5 μg oestradiol kg⁻¹.*

Treatment	Group size	Uterine weight (mg)	Uterine blood flow ml min⁻¹ /100 g	% Cardiac output to uterus
Oestradiol	10	100 ± 3	618 ± 37	0·95 ± 0·09
AH 7170 + mepyramine + cellulose sulph. followed by oestradiol	7	110 ± 7	112 ± 15*†	0·21 ± 0·03*†
Vehicle only	5	90 ± 3	55 ± 9*	0·07 ± 0·01*

* Values are significantly different from that for the oestradiol alone group ($P < 0·001$).

† Values are significantly different from that for the vehicle only group ($P < 0·05$).

pretreatment with an inhibitor of prostaglandin synthesis, AH 7170, used in conjunction with mepyramine maleate and cellulose sulphate. The compounds were all used in doses that would give a maximal effect without producing deterioration in the general health of the rat. Cellulose sulphate, at 1 mg kg⁻¹, produces a maximal depletion of kininogen in the rat within 60 min of injection (McCormick, Senior & Whalley, 1974). The dose of mepyramine maleate would normally provide histamine H_1-receptor antagonism (Szelenyi & Thiemer, 1977) and the dose of AH 7170 significantly reduces plasma concentrations of prostaglandin without interfering with plasma kinin concentrations (Phaily & Senior, 1978).

The results further substantiate the hypothesis that oestrogen-induced uterine hyperaemia in the rat is due to a complex series of events mediated through the interaction of histamine, prostaglandins and kinins. The time-course of the increase in blood flow (a maximal effect takes 1 h to occur) suggests that oestrogen is mobilizing or promoting synthesis of these local hormones within the uterine tissues. It has been shown that bradykinin may release prostaglandins under certain conditions (Palmer, Piper & Vane, 1973) and that inhibition of prostaglandin synthesis in the rat may modify the release of histamine during anaphylaxis (Engineer, Niederhauser & others, 1978). Thus, it can be seen that prostaglandins, histamine and kinins are capable of mediating in the response to each individual agent. No one local hormone seems to initiate the response, as inhibition of any one of these substances will only produce a 50% reduction in the oestrogen-induced uterine hyperaemia (Phaily & Senior, 1978). In an investigation involving several vasoactive compounds on the sheep uterine vascular bed, bradykinin was found to be the most effective compound tested in mimicking the effect of intra-arterial oestradiol (Resnick, Killam & others, 1975). It remains to be elucidated whether the blood flow response to oestrogen is mediated through uterine oestrogen receptors or through a separate mechanism.

We are grateful to Dr M. A. Stockham, Allen and Hanbury Research Ltd., for the gift of AH 7170.

April 19, 1978

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