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THE INFLUENCE OF AGROCLAVINE ON THE PREPARATION OF THE UTERUS FOR IMPLANTATION IN THE MOUSE

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The naturally occurring ergot alkaloid, agroclavine, interrupts pregnancy when administered to mated female mice in the diet at a non-toxic dosage for 2 to 3 days before implantation (Mantle, 1969). A similar action in the rat has also been reported (Edwardson & Macgregor, 1969), and the reversibility of the agroclavine implantation block by daily injections of progesterone suggests that the alkaloid may act either at the hypothalamic or ovarian level.

The investigation reported here was conducted to determine the effect of the alkaloid on the cellular changes in the uterus which precede implantation in the mouse.

During early pregnancy in the mouse, there is an abrupt change in the pattern of cell division in the uterus between the 3rd and 4th days after mating. On the 3rd day, large numbers of the epithelial cells of the lumen and glands, but very few of the stromal cells, are undergoing mitosis, whereas on the 4th day the situation is reversed (Finn & Martin, 1967). The influence of agroclavine treatment on uterine cell division during this phase of pregnancy has been studied.

Nulliparous females, strain BS/VS, were mated and the day on which a vaginal plug was found was designated Day 1 of pregnancy. Mice mated on the same day were divided into control and treated groups. Both groups were fed freely from Day 1 on Thompson's rat diet, the food of the treated group containing, in addition, 5 mg agroclavine/100 g. The mice were killed on the morning of Day 3 or Day 4, 2 hr after subcutaneous injection of 0·1 mg Colcemid (Ciba). The uteri were fixed in Bouin's fluid and sections prepared in the usual way. The number of cells undergoing mitosis in the three tissues of the endometrium was counted from a section taken at random from each uterus.

The results (Table 1) show clearly that the administration of agroclavine affects cell division during early pregnancy. There is no significant difference between the treated and control groups on Day 3 but on Day 4 the counts in the treated groups are significantly different from those in the control group in all the tissues of the endometrium. Furthermore, the stromal counts of the treated animals on Day 4 do not differ significantly from those of the control or treated animals on Day 3, indicating that the shift from epithelial to stromal cell division had not occurred. The change in the pattern of cell division in

normal pregnancy has been shown to be brought about by the secretion of progesterone (Martin & Finn, 1968; Finn & Martin, 1969), and it is considered to be an important factor in the preparation of the uterus for implantation (Finn, Martin & Carter, 1969).

These results provide further evidence that agroclavine interferes with the availability of progesterone, either by a direct effect on the corpora lutea or indirectly by reducing the secretion of prolactin by the pituitary.

TABLE 1

EFFECT OF AGROCLAVINE ON MITOSIS IN UTERINE TISSUES ON DAYS 3 AND 4 OF PREGNANCY

	Day of pregnancy	*No. of animals*	*Mean number of mitoses ± S.E.*		
			Epithelium		
			Lumen	*Glands*	*Stroma*
Control	3	8	5·5 ± 1·3	23·3 ± 1·2	3·9 ± 1·5
Agroclavine-treated	3	9	7·1 ± 2·2	20·1 ± 5·6	2·8 ± 1·0
Control	4	11	2·0 ± 2·0	0·4 ± 0·3	19·8 ± 4·1
Agroclavine-treated	4	11	11·9 ± 4·2*	14·2 ± 3·8**	5·7 ± 1·4**

* $P < 0.05$; ** $P < 0.01$.

The ovaries of the mice were also examined histologically, together with those from further groups of treated and untreated mice killed on Day 2 of pregnancy. Microscopic examination showed no obvious difference between the ovaries of the treated and untreated animals. The corpora lutea of the agroclavine-treated mice appeared to be morphologically normal, suggesting that the alkaloid had not interfered with luteal development. Structural development of the corpora lutea, however, does not necessarily imply that these bodies are functioning normally. There is evidence that the formation of corpora lutea follows ovulation spontaneously but that, at least in the mouse, further stimulation by prolactin is necessary for the secretion of progesterone (Nalbandov, 1964). The earlier finding that agroclavine inhibits lactation in mice, suggests that the alkaloid may interfere with the production of prolactin, and thus reduce progesterone secretion.

Apart from providing additional information about the mechanism of the implantation-inhibiting action of agroclavine, this investigation demonstrates how a quantitative assessment of uterine cell division can provide a simple guide to possible influences on uterine preparation for implantation.

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