PROGESTERONE INHIBITION OF MOUSE UTERINE EPITHELIAL PROLIFERATION

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Oestradiol stimulates uterine luminal epithelial cells of ovariectomized mice to pass through two rounds of cell division in quick succession (Das, 1972; Martin, Finn & Trinder, 1973). Progesterone injected with the oestrogen blocks entry of some cells into the first round of proliferation without affecting G₁*, S or G₂ in the remainder, but blocks entry of these cells into the second round. This suggested that cells were only sensitive to progesterone in early G₁ (Martin, Das & Finn, 1973). In the present experiment we attempted to delineate the sensitive period in greater detail.

Randomly bred albino mice were ovariectomized and primed as described previously (Das, 1972). Five days after priming they were separated into ten groups of three. All were given 50 ng oestradiol subcutaneously in 0.1 ml arachis oil at 0 h and 25 µCi [³H]thymidine ([³H]Thd; sp. act. 5 Ci/mm, Amersham) intraperitoneally in 0.1 ml 0.9% NaCl solution at 15 h. Group 1 also received 1 mg progesterone subcutaneously in arachis oil at 0 h, groups 2–9 received single injections of 1 mg progesterone at the times indicated in Fig. 1, and group 10, vehicle only at 0 h. All mice were killed at 29 h when many of the cells incorporating [³H]Thd at 15 h were in their second mitosis.

Procedures of fixation and autoradiography were as described by Das (1972). Numbers of [³H]Thd-labelled and unlabelled mitoses/section were estimated from ten sections from the mid-region of each uterus. [³H]Thd-Labelling and mitotic indices were estimated from 400 cells/uterus. Only nuclei with more than five grains were considered as labelled.

Estimates of the intermitotic phases of oestrogen-stimulated epithelial cells, obtained by Das (1972) from fractions of labelled mitosis (FLM) curves, were used for cells that were at the end of S at 15 h and in mitosis at 29 h, to calculate their positions in the intermitotic period at intervening times. Data are shown as mitotic indices and as mean number of labelled and unlabelled mitoses/section. All three expressions gave the same results. The data were not expressed as FLMs since the mitotic frequency was so low in most groups that FLMs were meaningless. Labelling indices ranged from 63–85% but showed no significant trend between groups and are not included. Given with oestrogen or up to 17 h later, progesterone reduced the number of mitoses at 29 h to zero or near zero, i.e. it arrested the entry of cells into

* G₁ is the interval between mitosis (M) and the beginning of the period of DNA synthesis (S) and G₂ is the interval between the end of S and M.
the second round of proliferation. It was also effective when given at 18 h, early in the second G₁, but completely ineffective when given late in this phase (20 h), or early in the second S-phase (21 h).

The results support the conclusion that progesterone only blocks uterine epithelial cells in early G₁ and is without effect upon their passage through late G₁, S and G₂. Stimulation of two rounds of division by one injection of oestrogen raises the possibility that cells might be committed to the second division some time before completing the first. This does not seem to be so since cells remained sensitive to inhibition up to a point early in second G₁. Progesterone needs to be present only for a short time to inhibit proliferation.

In oestrogen stimulated cells, G₁ is so short that accurate measurement of the sensitive part of G₁ was not possible.

REFERENCES