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# CILIATION IN ENDOMETRIAL EPITHELIUM OF THE RABBIT FOLLOWING OVARIECTOMY

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## Introduction

Little information has been reported on the effect of estrogen on morphological changes in the rabbit endometrium, in spite of a considerable amount of data accumulated on its progestational response. Only a few observations by scanning electron microscopy are available on the endometrium of the estrous and early postcoital rabbit.<sup>3,22,23,27</sup>

Our previous studies, by light (LM) and scanning electron microscopy (SEM), of the rabbit uterine and cervical epithelia during estrus, early pregnancy and pseudopregnancy suggested that the rabbit endometrium is much more responsive to ovarian hormones than is the cervical epithelium.<sup>40,41</sup> However, no histological investigations have been made on the uterine mucosa of ovariectomized rabbits, except for a study by LARSEN.<sup>24</sup> The present report deals with changes in the uterine epithelium of ovariectomized rabbits and of animals given estrogen, with or without progesterone, after ovariectomy.

## Materials and Methods

A total of 19 mature, female Japanese White rabbits were ovariectomized bilaterally under sterile conditions. Ten rabbits were killed at intervals of 3 months up to 18 months following operation — a pair of does at 3, 6, 9, and 12 months and one at 15 and 18 months, respectively. Six more spayed does were treated with estrogen, one at each of the six postoperative intervals from 3 to 18 months. Each of these does was injected subcutaneously (s. c.) with 5  $\mu$ gm of estradiol benzoate (Progynon B, Schering) in 1 ml of sesame oil every 12 hours for ten days, and then killed 12 hours after the last

injection. The remaining three does, spayed for 9, 12 and 15 months, respectively, and then given estrogen, were injected daily with 2 mg of progesterone (Upjohn) s. c. for the last three days of estradiol treatment.

The uteri were quickly removed from each rabbit immediately after sacrifice and were trimmed free of fat and extraneous tissue while being moistened with physiological saline solution. One member of each pair of uterine horns was assigned to LM and the other to SEM.

For LM, specimens were pinned on Sealant (Dow-Corning 780) and immediately fixed in Bouin's or Carnoy's solution. After a few hours, the specimens were cut into smaller segments which were placed separately in fresh fixative for a longer period. Paraffin sections of 5-7  $\mu\text{m}$  were stained with hematoxylin and eosin (H. E.) or azan, or by the periodic acid-Shiff (PAS) method.

For SEM, tissues taken from the mid-portion of the other uterine horn were cut open longitudinally and washed gently with physiological saline solution. The samples were then pinned on Sealant and pre-fixed with 3% glutaraldehyde in 0.1 M phosphate buffer at 4°C. After 24-hour fixation, the samples were dissected into smaller, appropriate segments, rinsed in phosphate buffer solution and post-fixed in 1% phosphate buffered osmium tetroxide for 1-1.5 hours at 4°C. The tissues were then washed in distilled water and dehydrated in a graded series of ethanol. Following dehydration, the samples were transferred to liquid CO<sub>2</sub> using isoamyl acetate as the intermediate fluid for critical-point drying. Dried tissues were fastened on brass stubs and sputter-coated with gold in an Ion Sputter (JFC-1100, JEOL, LTD.). Samples were examined with a JEOL JSM-20 or JSM-200 scanning electron microscope operated at 19 or 10 kV, respectively.

## Results

### Ovariectomized Rabbits

The size of each uterine horn decreased markedly to approximately 2 mm in diameter by 9 months after ovariectomy. The mucosal folds were also diminished in size.

In animals spayed for 3-6 months, the uterine mucosa showed corrugation of the luminal surface, characterized by a varying degree of reduction in height of the epithelial cells and fewer superficial uterine glands (Figs. 1, 2). The surface epithelium was composed of ciliated cells and atrophic, non-ciliated, peg-shaped cells (Fig. 2). Glandular epithelial cells were greatly diminished in size and arranged densely. In PAS- and azan-stained sections, mucus was no longer present within the epithelial cells after 3 months.

SEM demonstrated clearly the increased number of ciliated cells, which occupied half or more of the mucosal surface area (Fig. 3). The surfaces of non-ciliated cells were densely covered with small, nub-like microvilli, with occasionally a few short cilia (Fig. 4). Globular droplets were frequently found on the microvillous surface.

In animals spayed for 6 months, stromal cells, probably fibroblasts, were crowding just under the basement membrane and their nuclei were atrophic, showing pycnosis (Fig. 5). Free surfaces of non-ciliated cells had become hexagonal in appearance, and microvilli were smaller and fewer (Fig. 6). Frequently, several cilia of various lengths were apparent on the ciliated cells, on which microvilli were densely arranged, similar to those of fully ciliated cells (Fig. 7).

In rabbits spayed for 9 months, the mucosal surface was invaginated markedly and formed many recesses, probably due to atrophy of the sub-epithelial stroma (Fig. 8). LM and SEM demonstrated that the endometrial epithelium consisted almost entirely of ciliated cells, peg cells having disappeared (Figs. 8, 9).

In animals spayed for 12 to 18 months, the endometrium displayed a smooth surface (Figs. 10, 11). Cytoplasm within the epithelial cells was considerably decreased in amount and cell boundaries had become unclear. Ciliated cells had disappeared, but frequently microvillous cells had single, isolated cilia on their free surfaces (Fig. 12). Cytoplasmic protrusions were rarely observed on the apical surfaces of cells.

#### **Ovariectomized Rabbits Treated with Estrogen**

Estrogen administration to rabbits spayed for 3 to 9 months, in which uterine epithelium contained numerous ciliated cells, caused dramatic reduction in numbers of these cells (Fig. 13). However, estrogen treatment in rabbits spayed for 12 to 18 months led to an increase of ciliated cells in comparison to non-treated, spayed animals (Fig. 14).

There were various types of ciliated cells in the uterine epithelium in estrogen-treated animals regardless of the duration of spaying. Some ciliated cells displayed cilia of various lengths only at their central portions (Fig. 15), and some others showed relatively smaller numbers of cilia on their free surfaces (Fig. 16). In another case, stubby, short cilia appeared among microvilli (Fig. 17). Single, isolated cilia were not found in the endometrium of these animals.

Cell boundaries of the epithelial cells were distinct, because the apical surface of each non-ciliated cell had become convex. Microvilli were increased in thickness and distributed densely on the cell surface.

In LM, the epithelium was composed of tall-columnar ciliated and non-ciliated cells. In PAS- and azan-stained sections, non-ciliated cells contained abundant mucus in their supranuclear regions (Fig. 18). PAS-positive granules were also found in the subepithelial stroma and musculature. Abundant secretion was located in the uterine lumen. The endometrial stroma had become edematous and stromal cells were hypertrophic, consisting of a loose network of collagenous fibers interspersed with amorphous, non-staining stromal substance.

#### **Ovariectomized Rabbits Treated with Estrogen and Progesterone**

Uterine glands were slightly elongated as compared with those in animals treated with estrogen alone (Fig. 19). Numerous mitotic figures were found in both surface and glandular epithelium. Secretory material was never observed within the epithelial cells, but was occasionally found in the uterine lumen (Fig. 20). Microvilli were more densely distributed on the surfaces of non-ciliated cells, which frequently displayed cytoplasmic projections or buds (Fig. 21). Ciliated cells were diminished in number, and on ciliated cells there were fewer cilia per cell (Fig. 22).

#### **Discussion**

The present study showed that in rabbits spayed for 3 to 6 months, the non-ciliated cells were commonly peg-cell type in shape; whereas 9 months after spaying, the uterine epithelium was highly ciliated and peg cells, the common type of non-ciliated cell in these animals, had decreased considerably. This supports the general view that depleted secretory cells become peg cells and then are lost from the epithelium.<sup>5)</sup>

However, the widespread covering of cilia observed in animals spayed for 3 to 9 months has never, to our knowledge, been reported in the literature. LARSEN<sup>24)</sup> reported, using light and transmission electron microscopy, that the ciliated type of uterine epithelium disappeared in rabbits spayed for about 2 months. However, in the present study, loss of the ciliated cells from rabbit uterine epithelium occurred only after 12 to 18 months. Since stubby, short cilia, which resemble the immature or developing cilia reported by other investigators,<sup>2,11,12,33)</sup> were frequently present in these animals, it seems that ciliated epithelial cells in the rabbit uterus may originate not only by atrophy of the secretory cells, but also by ciliogenesis in the epithelial cells. And many of the non-ciliated cells, observed in animals spayed for 12 to 18 months, may be "deciliated" cells, because the cilia of remaining ciliated cells were discarded in part from their apical surfaces,

and peg cells (depleted secretory cells) were not seen any longer.

Exogenous estrogen administration to rabbits spayed for a relatively short period (3 to 9 months) led to considerable loss of ciliated cells. In addition, cells having stubby, short cilia were frequently noted. These observations suggest that ciliation, as well as deciliation, of individual cells occurs under the influence of estrogen. By contrast, estrogen treatment in rabbits spayed for a relatively long period (12 to 18 months) resulted in the reappearance of ciliated cells, whose number was larger than that seen in the estrous endometrium.<sup>3,22,23,40</sup> These results suggest that estrogen displays a dual effect on the ciliated cells of the rabbit endometrium: a stimulatory effect on the growth of cilia (ciliation or reciliation), and an adverse effect on the maintenance of cilia (deciliation).

According to the review on oviductal cilia by BRENNER<sup>5</sup>, estrogen induces both growth and neogenesis of the cilia. However, some reports on ciliary changes in human oviducts (see review by PAUERSTEIN<sup>32</sup>) and uteri<sup>14,15,35,36,42</sup> during the menstrual cycle are not consistent with this view.<sup>5</sup> Changes in ciliated cells of the human oviduct during the puerperium and after menopause have also been the subject of controversial reports.<sup>1,4,8,13,17,19,30,31,37</sup> In the oviducts of rabbits spayed and estradiol-treated, ODOR<sup>28</sup> and ODOR and BLANDAU<sup>29</sup> observed a striking deciliation of the ciliated cells, followed by reciliation. SHIPSTONE *et al.*<sup>38</sup> showed that the number of cilia in the rabbit oviduct increased at 70 hours after mating, when the estrogen level in ovarian venous plasma, as well as progesterone, should be at its nadir.<sup>21</sup> Also, an increase in ciliated cells had been shown to occur in the rabbit uterus 2 days after ovulatory stimulus.<sup>40,41</sup>

Treatment with progesterone following estrogen priming caused a decrease in the number of ciliated cells, as in the normal progestational endometrium in the rabbit,<sup>3,9,10,24,40,41</sup> and induced numerous mitotic figures in the uterine epithelium and glandular proliferation. This is in good agreement with the findings of LEE and DUKELOW<sup>25</sup>, who reported that both estrogen and progesterone are necessary for DNA synthesis and cell division in the rabbit uterus. From these observations, it is assumed that renewal of the epithelial cells does not occur frequently in the uterus under the influence of estrogen or of its withdrawal. Therefore, the present results suggest that individual epithelial cells in the rabbit uterus do undergo cyclic changes of ciliation, deciliation and mucus production or reciliation under certain conditions. There is a striking difference between the findings in the oviduct<sup>6,16,29</sup> and ours in the uterus. According to FLERKÓ<sup>10</sup>, hypertrophied "clear cells" can differentiate into either ciliated or secretory cells; while BRENNER<sup>5</sup>

and ODOR and BLANDAU<sup>29</sup>) believed that these cells give rise only to ciliated cells. However, cells that appear to be identical to the "clear cells" could not be found with our histological technique.

The present observations demonstrate that ovariectomy results in a complete cessation of secretory activity in rabbit endometrial cells. Following exogenous estrogen administration, uterine epithelium again produced and stored secretory material within the cells. An increased amount of secretory material was also evident in the uterine lumen, suggesting that a part of the secretion can be discharged under the influence of estrogen alone. This may be in harmony with the previous observations by BROWER and ANDERSON<sup>7</sup>) and HASHIMOTO *et al.*<sup>20</sup>), that the oviductal epithelium in the adult estrous rabbit displayed an active secretion. When estrogen priming was followed by progesterone in our study, secretory material was never seen within the epithelial cells and abundant secretion was located in the lumen. These observations strongly indicate that estrogen mainly induces the production of secretory granules in the cells, whereas progesterone causes their release rather than production, following the general concept documented for the mammalian oviduct.<sup>18</sup>)

Single, isolated cilia were found on the surfaces of the microvillous cells regardless of the time elapsed since spaying, but such single cilia disappeared after hormone treatment. The presence of the single, isolated cilium has been reported in the uteri of estrous rabbits<sup>3,40</sup>) and of rabbits 9-74 hours after ovulatory stimulus,<sup>27,41</sup>) and in the oviducts of rabbits under various conditions (in estrous<sup>4</sup>) and ovariectomized rabbits<sup>4,39</sup>), and in rabbits 24-72 hours after mating<sup>26</sup>). However, the function of the single cilium remains to be clarified.

This study provides evidence that estrogen is able to induce both ciliation and deciliation of the cells in the rabbit endometrial epithelium and suggests the possibility that the epithelial cells display individual cyclic variation: ciliation, deciliation, and mucus production or reciliation.

### Summary

The uterine epithelia of ovariectomized rabbits, and ovariectomized rabbits receiving estrogen with or without progesterone, were investigated with light and scanning electron microscopes. In rabbits spayed for 3 to 9 months, the uterine epithelium was profusely ciliated and the free surface of each non-ciliated cell was flat and hexagonal in appearance. Secretory material was no longer seen in the cells. In rabbits spayed for 12 to 18 months, ciliated cells had disappeared from the endometrium.

Estrogen given to these animals resulted in restoration of secretory activity in the secretory cells. The uterine epithelium of rabbits spayed for 3 to 9 months displayed a widespread deciliation due to estrogen administration, whereas estrogen treatment in rabbits spayed for 12 to 18 months caused reappearance of the ciliated cells. Progesterone following estrogen priming led to release of accumulated secretory material from the epithelial cells and loss of ciliated cells.

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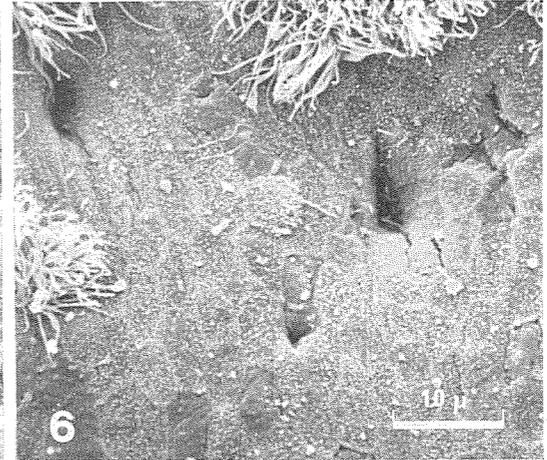
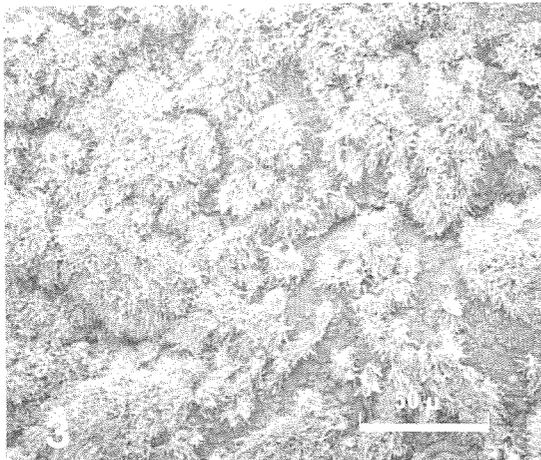
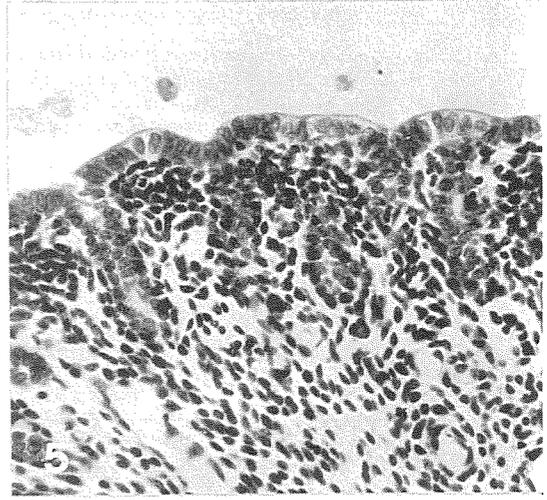
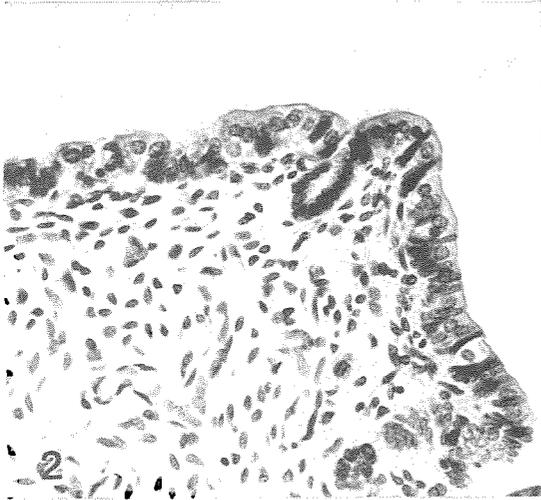
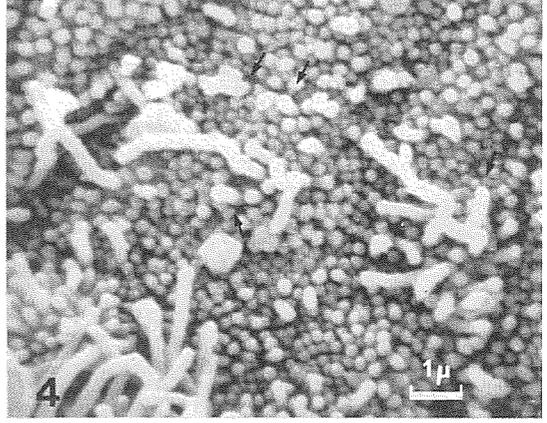
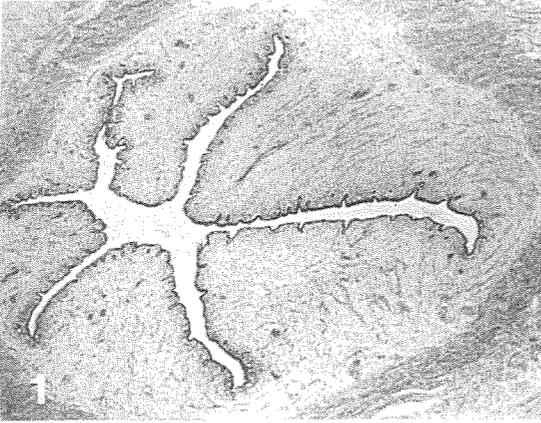
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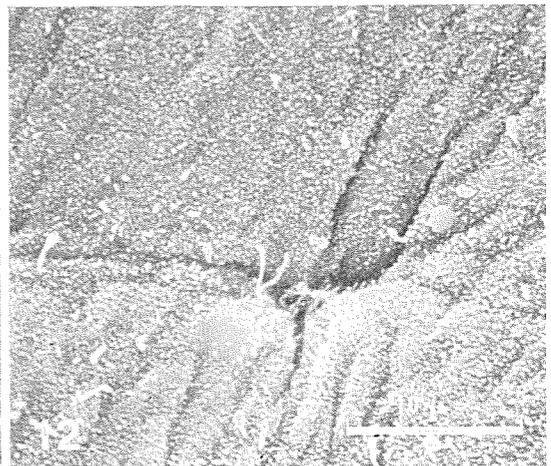
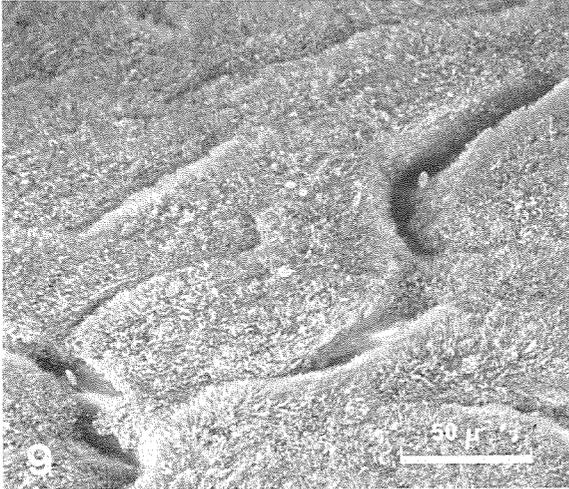
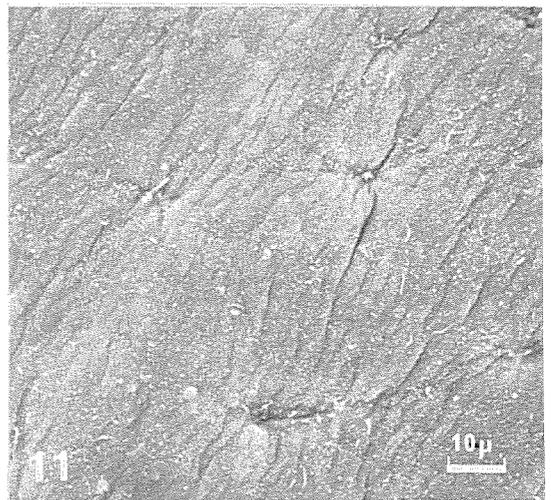
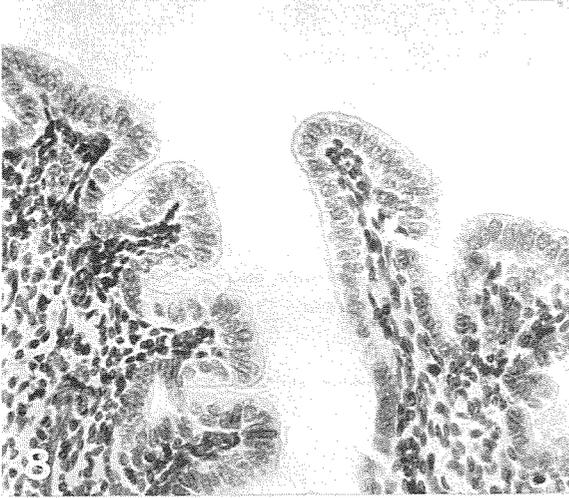
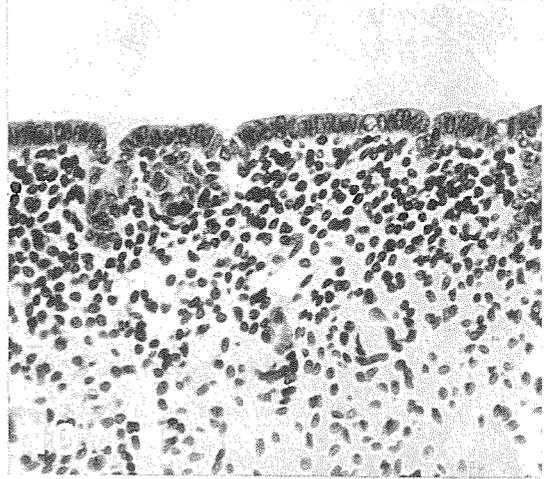
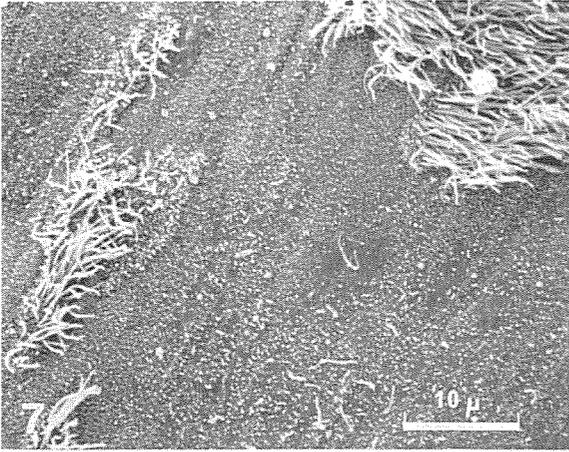
**PLATE 1**  
**EXPLANATION OF FIGURES**

- Fig. 1. Cross section of the uterus in rabbits spayed for 3 months, showing a small number of uterine glands. H. E.  $\times 25$
- Fig. 2. Surface epithelium of an area in Fig. 1, including ciliated cells and atrophic, non-ciliated cells. Uterine glands (arrow) are short and the lining epithelium is greatly atrophic. H. E.  $\times 325$
- Fig. 3. Surface feature of endometrium 3 months after spaying, showing numerous ciliated cells.
- Fig. 4. Higher magnification of an area in Fig. 3. The surfaces of non-ciliated cells are covered with abundant nub-like microvilli. Note some cilia or ciliary buds (arrows).
- Fig. 5. Histological appearance of uterine mucosa 6 months following ovariectomy, showing atrophy of subepithelial stroma. Relatively lucent cells in surface epithelium are ciliated cells. Almost all non-ciliated cells are peg-shaped. H. E.  $\times 325$
- Fig. 6. Surface epithelial feature of an area lacking cilia, 6 months after spaying. Non-ciliated cells have become hexagonal in surface appearance. Note their regressive features.



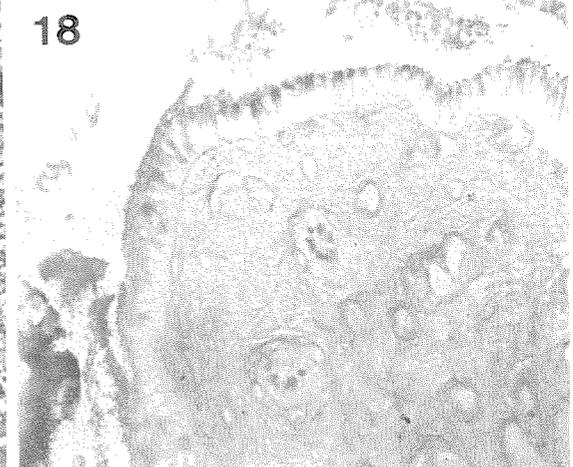
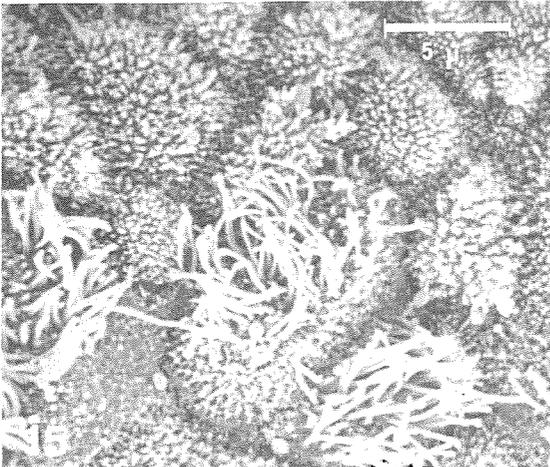
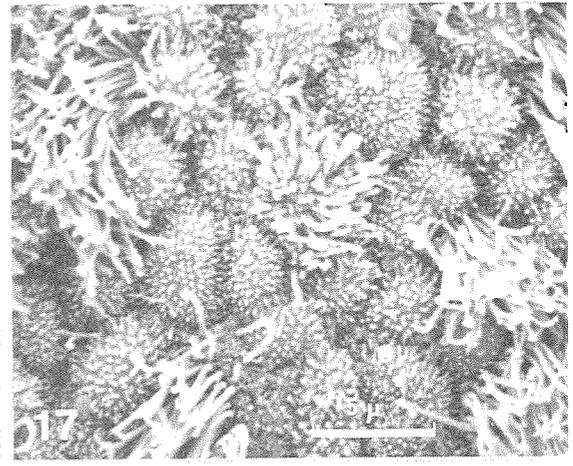
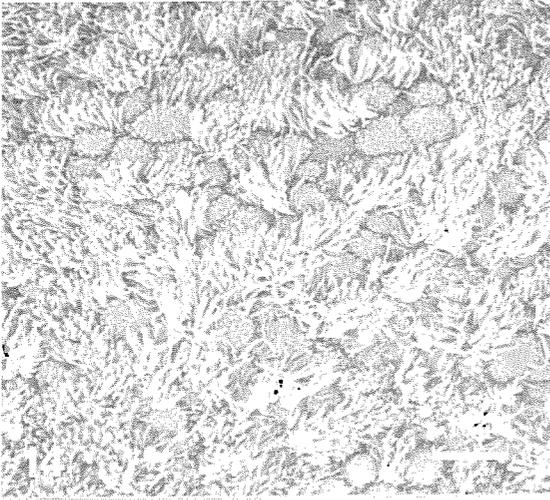
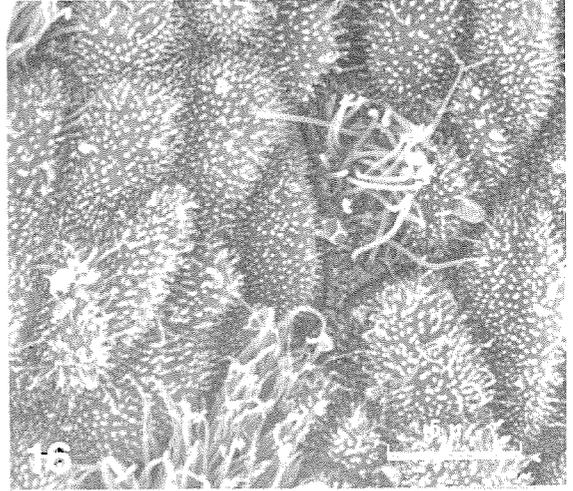
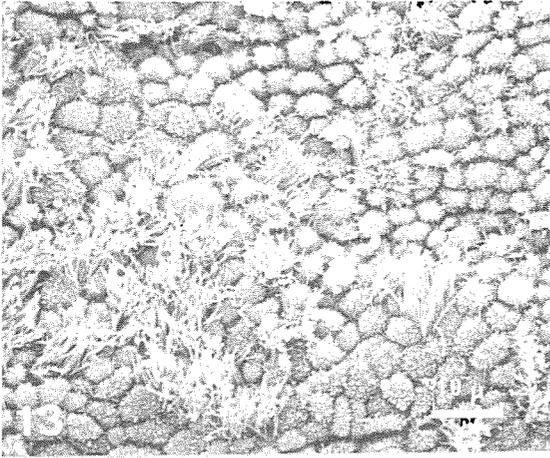
**PLATE 2**  
**EXPLANATION OF FIGURES**

- Fig. 7. Surface feature of endometrium, 6 months after spaying. Microvilli of the ciliated cells are more densely arranged than those of non-ciliated cells. Note single, isolated cilia.
- Fig. 8. Histological appearance of the endometrium, 9 months after spaying. The mucosal surface has invaginated, showing narrow recesses. H. E.  $\times 300$
- Fig. 9. Surface feature of endometrium, 9 months after spaying. The epithelium is almost completely ciliated. Note formation of crypts.
- Fig. 10. Histological appearance of the endometrium, 12 months after spaying. Mucosal surface is relatively smooth. Ciliated cells have been lost from the epithelium. H. E.  $\times 320$
- Figs. 11 & 12. Surface feature of the endometrium, 12 months after spaying. Invagination of the mucosal surface is shallow. Single, isolated cilia are still observed.



**PLATE 3**  
**EXPLANATION OF FIGURES**

- Fig. 13. Endometrial surface, 9 months after spaying and following estrogen treatment. A remarkable reduction in ciliated cells is evident in comparison with Fig. 9. Non-ciliated cells display convex apices.
- Fig. 14. Endometrial surface, 18 months after spaying and following estrogen treatment. Approximately half of the area of the epithelium is ciliated.
- Fig. 15. Epithelial cell surface, 3 months after spaying and following estrogen treatment. Note a cell having cilia only in the central portion.
- Fig. 16. Epithelial cell surfaces, 15 months after spaying and following estrogen treatment. Note a cell having fewer cilia.
- Fig. 17. Epithelial cell surfaces, 9 months after spaying and following estrogen treatment. Note cells having stubby, short cilia.
- Fig. 18. Histological features of endometrium, 12 months after spaying and following estrogen treatment. PAS-positive material is noted in the supranuclear region of epithelial cells and in the uterine lumen. The epithelium is composed of tall columnar cells. PAS.  $\times 160$



**PLATE 4**  
**EXPLANATION OF FIGURES**

- Fig. 19. Histological features of endometrium, 12 months after spaying and following estrogen and progesterone treatments. Uterine glands are developed and elongated. H. E.  $\times 80$
- Fig. 20. PAS-stained section of endometrium from the same rabbit as in Fig. 19. Secretory material cannot be recognized within the epithelial cells, but strongly positive material is located in the subepithelial stroma.  $\times 80$
- Fig. 21. Epithelial cell surfaces, 15 months after spaying and following estrogen and progesterone treatments. Non-ciliated cells display cytoplasmic projections or buds.
- Fig. 22. Epithelial cell surfaces, 9 months after spaying and following estrogen and progesterone treatments. Note cells displaying decreased number of cilia on the surface, from which microvilli have disappeared.

