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LYMPHATICS, INTRAEPITHELIAL LYMPHOCYTES AND ENDOMETRIAL LYMPHOID TISSUES IN THE RABBIT UTERUS: AN ELECTRON MICROSCOPIC AND IMMUNOHISTOLOGICAL STUDY

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ABSTRACT

Rabbit uterine intraepithelial lymphocytes, endometrial lymphoid aggregates and lymphatic capillaries were examined electron-microscopically and immunohistochemically at well-defined intervals after the injection of human chorionic gonadotropin (hCG). Lymphatic capillaries originated near the bases of the glands in the uterine cervix and in the border zone between the lamina propria mucosae and myometrium in the uterine body. The lymphatic capillaries were maximally dilated, and their endothelial cells were thinnest 8 hours after hCG injection. Patent junctions between the adjacent endothelial cells of lymphatics in the uterine body were observed in good accordance with the appearance of stromal edema and lymphatic dilatation. The numbers of intraepithelial lymphocytes and macrophages changed cyclically after the induction of ovulation. They were highest 11 hours after hCG injection when lymphocytes were seen occasionally in the lumens of lymphatics located in the lamina propria mucosae of the uterine body. Most of the intraepithelial and interstitial lymphocytes were cells labeled with T cell serum but some were labeled with IgA serum and were occasionally seen beneath the epithelium. Lymphoid aggregates were uniformly present in the stratum basalis and consisted of lymphocytes and macrophages. They had no germinal centers, surrounding lymphatics or high endothelial venules (HEV).

The results suggest that lymphatic capillaries are the main route for the removal of edema fluid and for migratory lymphoid cells in the rabbit uterus.

The few studies that have been done on the intraepithelial lymphocytes in the bovine uterus (1) and on the endometrial lymphoid tissue in the human uterus (2) have shown cyclical changes in the number of intraepithelial lymphocytes and lymphocyte subpopulations in the lymphoid tissue during the estrous cycle. Barker and Billingham (3) have suggested that lymphatic drainage influences the host's immune response because the interruption of lymphatic drainage to regional nodes interferes with the rejection of allografts. However, the lymphatic function and ultrastructural changes noted in the rabbit ovary (4,5) have not been confirmed in the uterus during the menstrual cycle. In the present study, cyclical ultrastructural changes of the lymphatics, endometrial lymphoid aggregates and the number of intraepithelial lymphocyte subpopulations were studied in the rabbit uterus after the induction of ovulation.

MATERIALS AND METHODS

Twenty mature female rabbits weighing about 2kg were injected with 100i.u.

human chorionic gonadotropin (hCG) intravenously; ten control rabbits received no hCG. Eighteen rabbits were used for the light and electron microscopic study and the rest for the immunohistochemical study. Rabbits ovulated regularly about 10-12 hours after hCG injection; ovulatory failures were extremely uncommon. Four, 6, 8, 11 hours, and 7 and 21 days after hCG injection, the rabbits were anesthetized intravenously with sodium pentobarbital (30mg/kg body weight).

For light and electron microscopy, the uterus was isolated after fixation by arterial perfusion first with 200ml of heparinized saline and then with 500ml of 1% paraformaldehyde and 1.25% glutaraldehyde in 0.1M phosphate buffer (PB), pH 7.35. Specimens were taken from the middle portion of the horns and the cervical region, cut into small pieces and postfixed with 1% osmium tetroxide in 0.1M PB. The specimens were then dehydrated in the usual way and embedded in Epon. Serial semi-thin sections (1μm thick) were stained with toluidine blue for light microscopy, and thin sections (60-80nm thick) were double-stained with uranyl acetate and lead citrate for electron microscopy.

The lymphocytes in a 2mm long specimen of uterine epithelium, oriented with the plane of the sections passing vertically through the epithelium, were examined in 4 separate semi-thin sections at each period after hCG injection and counted on montages at a final magnification of 200x. The diameter of 10 lymphatic capillaries and the endothelial thickness were examined in more than 10 separate thin sections at each period and measured on montages with the plane of the vertical sections through the lumen at a final magnification of 3,000x and 10,000x, respectively. The endothelial thickness was measured in the non-nuclear cytoplasm.

For immunohistochemistry, the following commercially available antisera were used: monoclonal mouse anti-rabbit T cell (UCB, Belgium), IgA, IgG, and IgM sera (Nordic, Belgium) in dilutions of 1:200 to 1:500 with phosphate buffered saline (PBS) containing 1% normal goat serum (NGS). The rabbits were perfused via the abdominal aorta first with 200ml of heparinized saline and then with 500ml of a solution containing 0.05% glutaraldehyde, 4% paraformaldehyde and 0.2% picric acid for electron microscopic preparations. The uterus was removed after the perfusion, cut into small pieces and kept for 3 hours in the same fixatives. Fixed materials were rinsed in increasing concentrations of sucrose in 0.1M PB, frozen in liquid nitrogen, immersed in 0.1M PB and cut into serial sections 40-60μm thick on a Dosaka microslicer at 4°C. Before incubation in the various antisera, sections were washed 3 times in 0.01M PBS and incubated with 20% NGS in 0.01M PBS for 1 hour at room temperature. After incubation for 12 hours in the various monoclonal antisera at 4°C, sections were washed with 1% NGS in 0.01M PBS for 30 minutes at 4°C and further incubated with goat anti-mouse IgG conjugated to horseradish peroxidase (DAKO, Denmark) diluted 1:100 with 1% NGS in 0.01M PBS for 3 hours at room temperature. Sections were rinsed 3 times in 0.01M PBS and twice in 0.05M Tris-HCl buffer, pH 7.6 for 30 minutes at 4°C. Sections were incubated with a solution of 3',3'-diaminobenzidine tetrahydroxychloride (DAB) (Sigma, USA) containing 0.05% DAB, 0.01% H_2O_2 in 0.05M Tris-HCl at pH 7.6 for 5 to 10 minutes at 4°C to reveal any peroxidase activity. The sections were postfixed with 1% osmium tetroxide in 0.1M PB for 1 hour at room temperature, further stained with 1% uranyl acetate in 70% ethanol for 40 minutes, and then dehydrated and embedded in Epon. Cells labeled with T cell, IgA, IgG and IgM sera were examined with an electron microscope.

RESULTS

The mean transverse diameter of the cervical regions and the middle portions of the horns was 9mm and 3mm, respectively. The uterus fixed by arterial perfusion contained two types of vessels; vessels with a lucent lumen and vessels with a toluidine blue lightly stained lumen

Table 1
Mean Diameter of Lymphatic Capillaries[a]

Intervals after hCG injection	0 hr	4 hrs	6 hrs	8 hrs	11 hrs	1 w	3 ws
Mean diameter	13.7±3.4	29.0±12.6	28.6±11.8	40.4±9.2	16.9±5.3	20.4±6.3	15.2±3.8
Minimal diameter	10.6	15.0	15.4	26.8	12.7	14.1	10.1
Maximal diameter	19.6	47.1	45.9	50.0	23.6	29.5	16.3

[a]Values are expressed in micrometers

under light microscopy. Electron microscopy confirmed that the former (lucent lumen) were blood vessels and the latter (blue lumen) were lymphatics.

Before hCG injection

Intrauterine lymphatics were distributed in the lamina propria mucosae, myometrium and subserous layer. Lymphatic capillaries originated near the bases of the glands in the uterine cervix *(Fig. 1)*, and in the border zone between

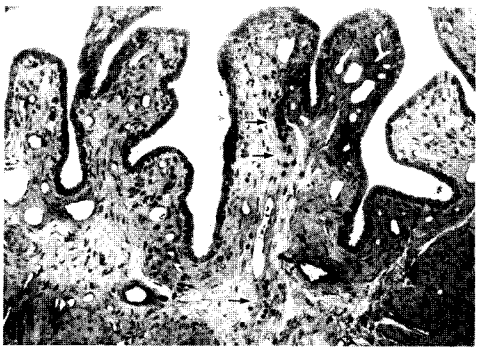

Fig. 1. Part of uterine cervix before hCG injection. Lymphatic capillaries (arrows) can be seen in the lamina propria mucosae near the bases of the glands and contain many lymphoid cells in the lumens. x200.

the lamina propria mucosae and myometrium in the uterine body. They showed a variety of shapes and calibers from 10.6 to 19.6μm (average 13.7μm, *Table 1*). The endothelial cells averaged 0.64μm in thickness and were thinner than those of the blood capillaries of which the mean thickness was 1.23μm. Lymphatic endothelial cells were flat on the luminal surface but extended small projections into the surrounding tissue in which fine intracellular filaments about 6nm in diameter were concentrated showing hemi-desmosome-like apparatuses *(Fig. 2)*. The features and distribution of intracellular organelles, except abundant lysosome-like

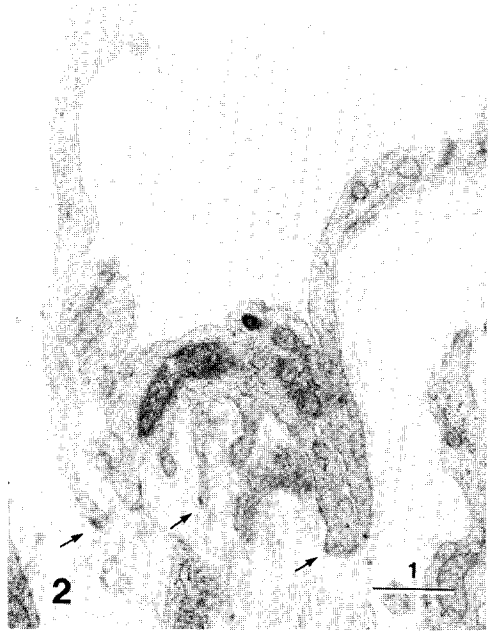

Fig. 2. Part of a large lymphatic vessel in the subserous layer of the uterine body before hCG injection. Small projections with hemidesmosone-like apparatuses (arrows) extend at places from the lymphatic endothelial cell into the surrounding tissue and contains abundant free ribosomes and vesicles. The lumen is filled with dark amorphous material. The discontinuous basal lamina can be seen beneath the endothelial cells. x15,800, Bar: 1μm.

dense bodies in the lymphatic endothelial cells, were similar to those in other organs. The basal lamina was discontinuous or absent. No pericytes were seen beneath the endothelial cells. Adjacent endothelial cells showed overlapping or

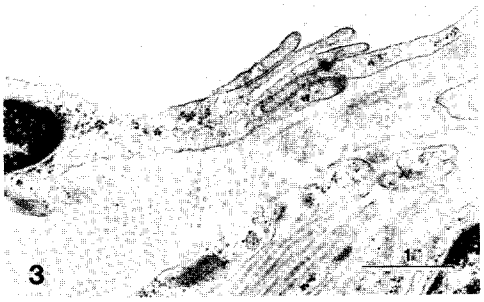

Fig. 3. Part of a lymphatic capillary in the lamina propria mucosae of the uterine body before hCG injection. The adjacent endothelial cells show interdigitation which is a common junctional mode, as well as overlapping in lymphatic capillaries. No basal lamina or pericytes can be seen beneath the endothelial cells. x23,600, Bar: 1 μm.

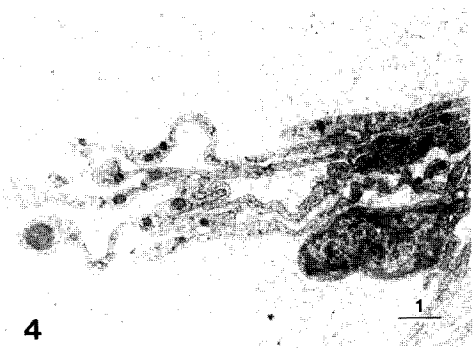

Fig. 4. Part of the valve of a lymphatic vessel of the uterine body before hCG injection. The endothelial cells contain many vesicles and free ribosomes and moderate numbers of lysosome-like dense bodies and mitochondria. The basal lamina is sporadically present beneath the endothelium. x9,900, Bar: 1 μm.

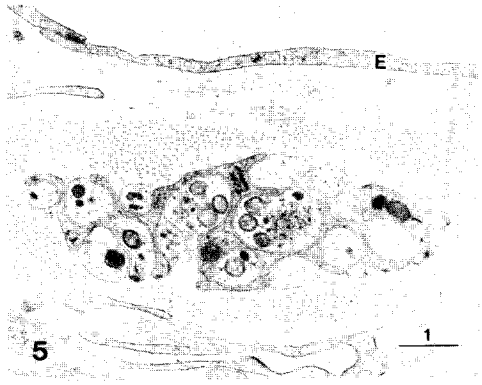

Fig. 5. Part of a lymphatic capillary in the myometrium of the uterine body before hCG injection. An unmyelinated neuron fiber containing vesicles of various sizes and electron densities can be seen beneath the endothelium (E). x15,200, Bar: 1 μm.

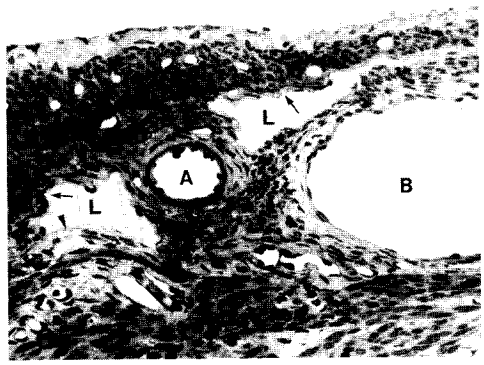

Fig. 6. Lymphatics (L) showing irregular lumens in the myometrium of the uterine body before hCG injection. Smooth muscle cells (arrows) and collagen fiber bundles (arrowhead) are aggregated beneath the endothelium. Arteriole (A), Blood capillary (B). x400.

simple interdigitation *(Fig. 3)*, but no patent junctions. No edema was observed in the perivascular area. Lymphatics in the myometrium and subserous layers sometimes had valves and well-defined basal lamina in the valve areas *(Fig. 4)*. Lymphatics were in close contact with unmyelinated nerve fibers *(Fig. 5)*, dense collagen fiber bundles and occasionally an aggregation of smooth muscle cells instead of collagen fiber bundles *(Fig. 6)*. A few lymphocytes were seen in the epithelium and lamina propria mucosae *(Fig. 7)*. The mean lymphocyte number was 21.2 in the epithelium *(Table 2)*. Lymphoid aggregates were present exclusively in the stratum basalis and had no germinal centers, surrounding lymphatics or HEV *(Fig. 8)*. Their structures consisted of lymphocytes and macrophages *(Fig. 9)*. The lymphocytes contained electron-dense cytoplasm because of abundant free ribosomes and moderate numbers of mitochondria, whereas the macrophages

Table 2
Mean Number of Intraepithelial Lymphocytes[a]

Intervals after hCG injection	0 hr	4 hrs	6 hrs	8 hrs	11 hrs	1 w	3 ws
Mean number	21.2±5.9	22.4±8.6	50.8±12.2	48.2±17.1	98.6±29.7	5.4±2.7	21.4±5.5
Minimal number	13	14	35	34	73	2	16
Maximal number	27	35	69	76	145	9	29

[a]Values are expressed in the numbers of lymphocytes in a 2mm length of the uterine epithelium

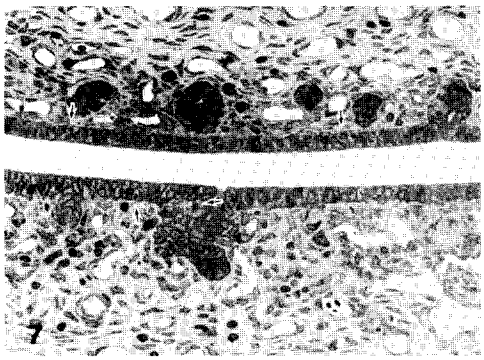

Fig. 7. A few intraepithelial lymphocytes (arrows) of the uterine body before hCG injection. Note the smooth basal side of the epithelium in contrast to that in Figs. 15 and 16. *x400.*

had electron-lucent cytoplasm with moderate numbers of phagosomes and lysosome-like dense bodies.

After hCG injection

The distribution of the intrauterine lymphatics after hCG injection was the same as that before hCG injection. No substantial difference of ultrastructural changes in lymphatics between the cervical region and uterine body was noted at each interval after hCG injection. Lymphoid aggregates were constantly present in each stage.

1. Four hours after hCG injection: Blood capillaries with closed fenestrae, which were never seen before hCG injection, were sporadically present in the lamina propria mucosae of the uterine body *(Fig. 10)*. Lymphatic capillaries averaged 29.0μm in diameter and were

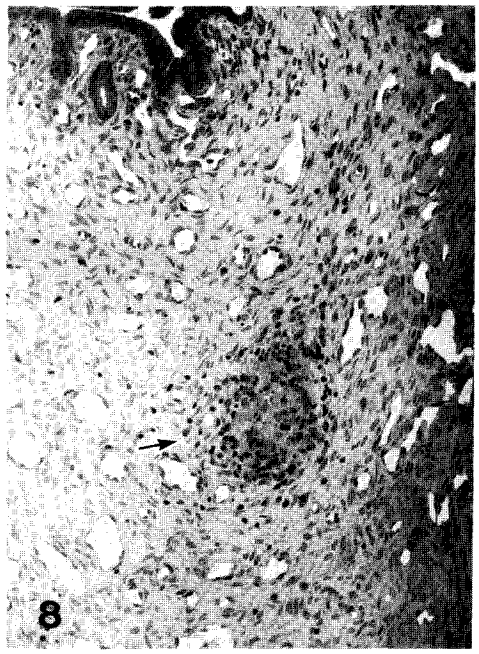

Fig. 8. Lymphoid aggregates (arrow) in the lamina propria mucosae in the uterine body before hCG injection. No lymphatic capillaries or high endothelial venules can be seen around or within the aggregates. x200.

larger than those before hCG injection *(Table 1)*, while the endothelial thickness was the same as before hCG injection (mean thickness 0.63μm). Macrophages were more numerous in the endometrium and often passed through the intercellular clefts between the epithelial cells, and the major part of the cytoplasm occupied by a nucleus and abundant cellular organelles extended into the uterine lumen *(Fig. 11)*. The number of intraepithelial

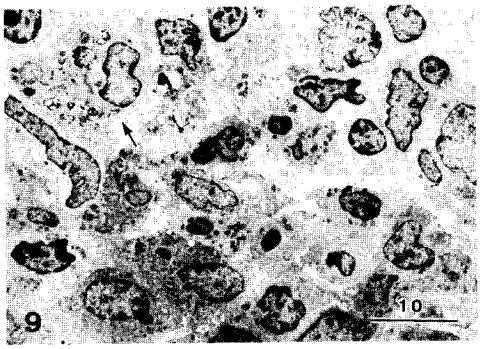

Fig. 9. The cells composing the lymphoid aggregates seen in Fig. 8 *are lymphocytes and macrophages (arrow). Lymphocytes show electron-dense cytoplasm because of abundant ribosomes, whereas the cytoplasm of macrophages is electronlucent and contains moderate numbers of phagosomes and lysosome-like dense bodies. x1,600, Bar: 10μm.*

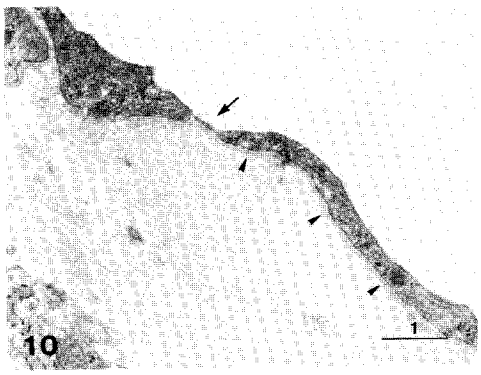

Fig. 10. Part of a blood capillary in the lamina propria mucosae of the uterine body 4 hours after hCG injection. The endothelium shows a fenestra with diaphragm (arrow). The well-defined basal lamina (arrowheads) is continuously present beneath the endothelium. x16,800, Bar: 1μm.

lymphocytes was similar to that before hCG injection (average 22.4, *Table 2*).

2. Six hours after hCG injection: Perivascular edema became prominent, corresponding to the increase of fenestrated blood capillaries in the lamina propria mucosae. The mean diameter of lymphatic capillaries in the lamina propria mucosae of the uterine body was 28.6μm and the same as that 4 hours after hCG injection *(Table 1)*. The endothelial cells were slightly thinner than at 4 hours after

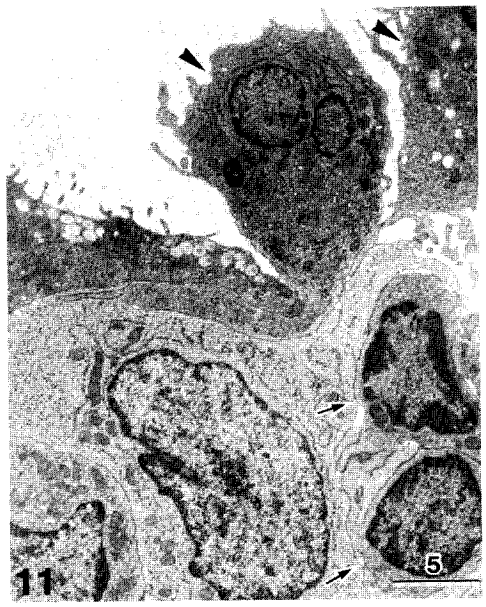

Fig. 11. Two lymphocytes (arrows) and two macrophages (arrowheads) passing through the epithelium of the uterine body 4 hours after hCG injection. The major part of the cytoplasm of the macrophage seen in the uterine lumen extends fine projections and contains two nuclei, abundant free ribosomes, moderate numbers of mitochondria, rough endoplasmic reticulum and vesicles. x7,300, Bar: 5μm.

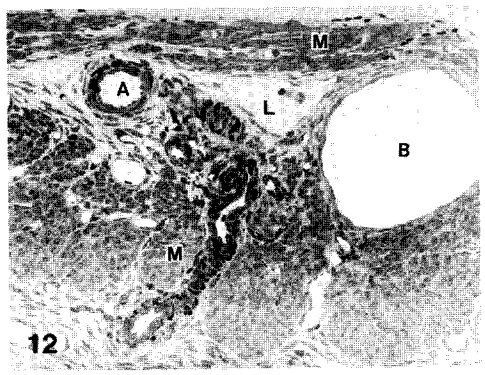

Fig. 12. The muscular layer in the uterine body 6 hours after hCG injection. Three lymphoid cells can be seen in the lumen of a lymphatic (L). Muscular layer (M), Arteriole (A), Blood capillary (B). x350.

hCG injection (mean thickness, 0.57μm). A few lymphocytes were observed in the lumens of the lymphatics in the muscular layer *(Fig. 12)* and lamina propria mucosae *(Fig. 13)* of the uterine body. There

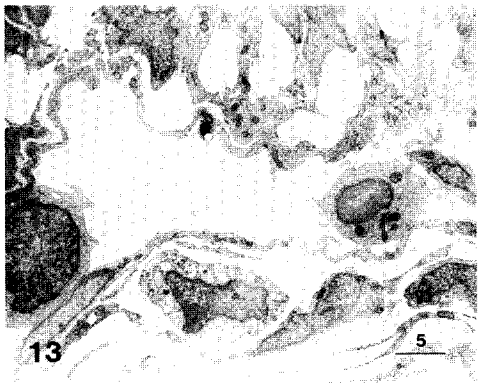

Fig. 13. Two lymphocytes can be seen in the irregular lumen of a lymphatic capillary, and an unmyelinated neuron fiber is present beneath the endothelium in the lamina propria mucosae 6 hours after hCG injection. x6,200, Bar: 5μm.

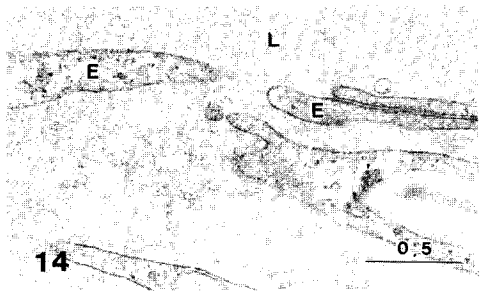

Fig. 14. Part of a lymphatic capillary (L) in the border zone between the lamina propria mucosae and myometrium of the uterine body 8 hours after hCG injection. Flocculent material seen beneath the endothelium can be followed into the lumen through a patent junction between apposing endothelial cells (E). x48,000, Bar: 0.5μm.

were more lymphocytes and macrophages in the epithelium and lamina propria mucosae than at 4 hours after hCG injection (mean number of intraepithelial lymphocytes was 50.8, *Table 2*).

3. Eight hours after hCG injection: The uterus was larger because of stromal edema than that before hCG injection. The transverse diameter of the cervical region and middle region of the horns averaged 13mm and 4.5mm, respectively. Patent junctions were observed between adjacent endothelial cells of the lymphatics in the uterine body *(Fig. 14)*. The lymphatic capillaries, occasionally containing lymphoid cells in the lumen,

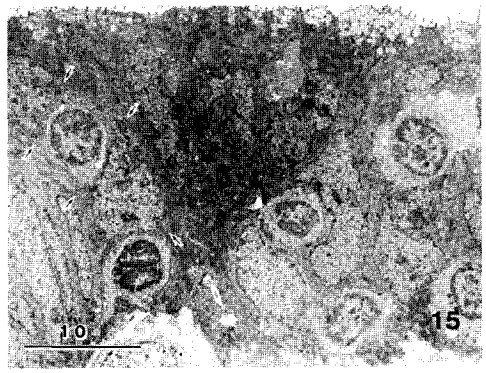

Fig. 15. Ten lymphocytes passing through the epithelium of the uterine body 8 hours after hCG injection. The intraepithelial lymphocytes have electron-lucent cytoplasm, whereas that of lymphocytes in lymphoid aggregates is electron-dense, as shown in Fig. 9. *Epithelial cells extend their cytoplasm into the interstitial tissue at this stage. A lymphocyte can be observed within the cytoplasm of the epithelial cell (arrows). x2,500, Bar: 10μm.*

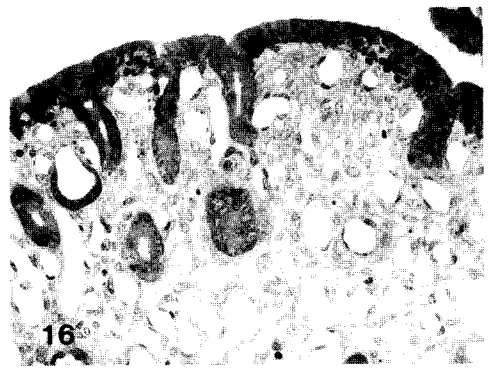

Fig. 16. Many intraepithelial lymphocytes invade the uterine epithelium in clusters 11 hours after hCG injection. x4,400.

were maximally dilated and their endothelial cells were thinnest at this stage; the mean diameter *(Table 1)* and thickness were 40.4μm and 0.52μm, respectively. The number of intraepithelial lymphocytes was similar to that at 6 hours after hCG injection (average 48.2, *Table 2*). These lymphocytes passed through the epithelium intra- or intercellularly *(Fig. 15)*. The number of lymphocytes passing through the cytoplasm of epithelial cells was only 4 among 40 lymphocytes count-

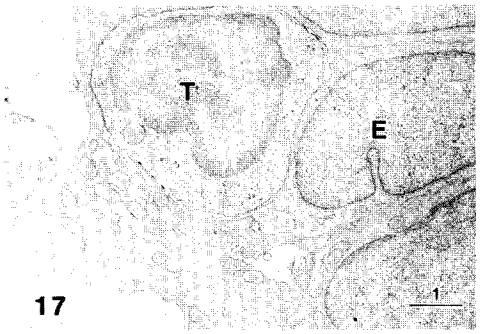

Fig. 17. A cell labeled with anti-rabbit T cell serum (T) in the uterine epithelium 11 hours after hCG injection. DAB reaction products are localized only on the cell membrane and not in the cytoplasm. Epithelial cell (E). x14,500, Bar: 1μm.

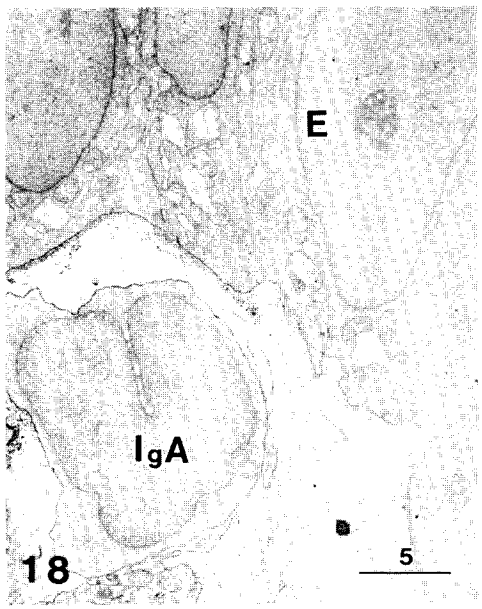

Fig. 18. A cell labeled with anti-rabbit IgA serum (IgA) showing DAB reaction products on the cell surface beneath the uterine epithelium 11 hours after hCG injection. The localization of DAB reaction products and fine structures of the cell are very similar to those of the cell labeled with T cell serum in Fig. 17. *Epithelial cell (E). x8,400, Bar: 5μm.*

ed on electron micrographs.

4. Eleven hours after hCG injection (ovulatory stage): Lymphatic capillaries averaged 16.9μm in diameter *(Table 1)* and the endothelium 0.56μm in thickness. The patent junctions seen at 8 hours after hCG injection were not noted between adjacent endothelial cells. Lymphocytes and macrophages were occasionally seen in the lumen of the lymphatics in the lamina propria mucosae in the uterine body. Infiltration of lymphocytes into the epithelium was most conspicuous at this stage *(Fig. 16)*, and the mean number of lymphocytes was 98.6 *(Table 2)*. Most of them in the epithelium as well as in the lamina propria mucosae were cells labeled with T cell serum, but not IgA, IgG or IgM serum, in immunoelectron-microscopic studies *(Fig. 17)*. However, a few cells labeled with IgA serum but not T cell serum were seen beneath the epithelium *(Fig. 18)*.

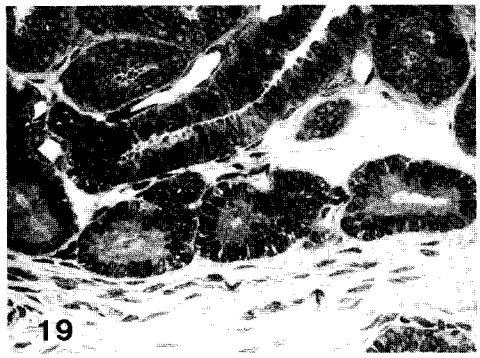

Fig. 19. The uterine epithelium 7 days after hCG injection. Intraepithelial lymphocytes are much fewer at this stage than at 11 hours as shown in Fig. 16. *x390.*

5. Seven days after hCG injection: The size of the uterus was only slightly greater than that before hCG injection. The mean transverse diameter of the cervical region and middle region of the horns was 10mm and 3.5mm, respectively. No edema was noted around lymphatics in the lamina propria mucosae. The lymphatic capillaries averaged 20.4μm in diameter *(Table 1)* and 0.65μm in endothelial thickness. The form and structure of the lymphatic capillaries had resumed their pre-injection appearance. The intraepithelial lymphocytes were notably few at this stage *(Fig. 19)*, with a mean number of 5.4 *(Table 2)*.

6. Twenty one days after hCG injection: Lymphatic capillaries averaged 15.2μm in diameter *(Table 1)* and 0.68μm in endothelial thickness. The mean number of intraepithelial lymphocytes was 21.4 *(Table 2)*. Thus, the findings at this stage were very similar to those before hCG injection.

DISCUSSION

A number of studies using a variety of tracing techniques have been carried out on the distribution of intrauterine lymphatics in the rat (6), mouse (7), and rabbit (8), and the results indicate an absence of lymphatic vessels in the rodent uterine endometrium. However, Fabian (9), Wislocki and Dempsey (10) have reported the presence of lymphatics in the mouse and monkey uterine endometrium, respectively. The controversy is due to the difficulty of correctly identifying lymphatics under light microscopy, the disadvantages of the tracer entering veins and considerable extravasation of tracer into tissue spaces. Electron microscopic observations have confirmed the characteristics of lymphatic capillaries described by Leak (11) and the differences between blood and lymphatic capillaries (4). Head and Seelig (12) have recently reported the presence of lymphatic capillaries in the rat endometrium using electron microscopy. The results of our electron microscopic studies are almost identical, but show differences in the distribution of lymphatic capillaries between the uterine cervix and body. In the present study, lymphatic capillaries are seen to originate near the bases of the glands in the uterine cervix and in the border zone between the lamina propria mucosae and the myometrium in the uterine body. These findings suggest that antigenic foreign substances in the uterine lumen have difficulty directly entering the lymphatics, which are at a considerable distance from the epithelium. The most interesting finding was the presence of macrophages in the epithelium. Because the macrophages occasionally extend a major part of their cytoplasm into the uterine lumen, they probably play an important role as antigen-presenting cells.

The diameter, endothelial thickness and junctional mode of lymphatic capillaries changed cyclically in the rabbit uterus after hCG injection. These data are similar to those of the rabbit ovary (4,5), but the dilatation of the intrauterine lymphatics was less and began later than that of the intraovarian lymphatics: the maximal mean diameter of the intrauterine lymphatics was 40.4μm 8 hours after hCG injection and that of the intraovarian lymphatics was 99.9μm 4 hours after hCG injection. The degree of dilatation of the lymphatics correlated well with the macroscopic size of the uterus, the amount of stromal edema and the appearance of patent junctions. The above findings suggest the function of the uterine lymphatics is the same as that in the rabbit ovary (4,5); that is, they provide a major route for the removal of edema fluid.

The number of intraepithelial lymphocytes changed cyclically after the induction of ovulation. The number of lymphocytes increased dramatically 11 hours after hCG injection (ovulatory stage) to about 5 times that before hCG injection. In contrast, the number in the bovine uterus changed only slightly during the estrous cycle: from 19.7 to 28.2 (1). Most of the lymphocytes in the epithelium and the lamina propria mucosae were labeled with T cell serum but not IgG, IgA, or IgM serum; these lymphocytes may be mainly suppressor T cells, as reported in the human uterine endometrium (13), in the epithelium of the human oviduct (14) and in sheep uterine lymph (personal observations). The above description of the hormonal changes indicate that the variation of the hCG level in the blood probably affects the number of intraepithelial T cells. These cells, presumably suppressor T cells as reported by Head et al (12) and Daya et al (13), in cooperation with macrophages and B lymphocytes in the lamina propria mucosae, may prevent the immune response to

antigens expressed on foreign substances. Such suppressive activity may play an essential role in local immunoregulation in the uterus.

It has previously been established by Morris et al (2) that endometrial lymphoid tissue in the human uterus is present at three sites: intraepithelial lymphocytes, interstitial lymphocytes with macrophages, and lymphoid aggregates with germinal centers in the stratum basalis. They claim that antigen-primed lymphocytes and macrophages in the surface or gland columnar epithelium migrate to the lymphoid aggregates in the stratum basalis where further amplification of the immune response can occur, and then to regional and central lymphoid tissues. Their findings have shown convincingly that human endometrial lymphoid tissue is morphologically similar to mucosal lymphoid tissues elsewhere in the body. However, rabbit endometrial lymphoid aggregates have no germinal centers surrounding lymphatic capillaries or HEV, and seem to be simply lymphocyte infiltrations. We have reported earlier that lymphatic capillaries and HEV, occasionally containing various lymphocyte subsets, are uniformly present in the rat gut-, and bronchus-associated lymphoid tissues and serve as important pathways for migratory lymphoid cells in lymphatic tissues (15,16). The presence of lymphatic capillaries and HEV, however, was not noted in rabbit endometrial lymphoid tissues. Therefore, the rabbit lymphoid aggregates while they are a source of intraepithelial and interstitial lymphocytes, are probably not the site for the microcirculation of migratory lymphoid cells or amplification of the immune response. The routes of migratory lymphoid cells are not apparent from our study. Nevertheless, we have noted lymphocytes entering the lumen of the lymphatics in the lamina propria mucosae of the uterine cervix and body. These findings raise the possibility that intrauterine lymphatics are the main route for migratory lymphoid cells as well as for removal of surplus edema fluid.

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