ELECTRON MICROSCOPY OF THE UTERINE EPITHELIUM IN THE RABBIT

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ABSTRACT

The ultrastructure of the uterine epithelium has been studied in estrous, ovariectomized, pregnant, and pseudopregnant rabbits. Tissue for light microscopy was fixed in Bouin's solution and stained with hematoxylin and eosin, by the periodic acid–Schiff (PAS) method, and with methylene blue. Tissue for electron microscopy was fixed in 1 per cent osmium tetroxide in White's saline and embedded in Araldite. The uterine epithelium in estrus is comprised of ciliated and non-ciliated cells. After ovariectomy the epithelium becomes reduced in height and PAS-positive material disappears. Multinucleated cells are formed in the epithelium in pregnancy, pseudopregnancy, and in the non-pregnant horn in unilateral pregnancy. They degenerate during the 3rd week of pseudopregnancy and during the 4th week of pregnancy in the non-pregnant horn. The formation of multinucleated cells is believed to be under hormonal control. The uterine epithelium in contact with the blastocyst changes into a "symplasma," presumably under the influence of a local (chemical?) effect produced by the blastocyst. This change is not seen in pseudopregnancy nor in the non-pregnant horn in unilateral pregnancy. A complex infolding of the basal cell membrane of the epithelium accompanies the "symplasmic" change. The remaining uterine epithelium in pregnancy shows a well developed ergastoplasm suggesting a production of secretion materials, some of which may be available for absorption by the fetus through the yolk sac or paraplacental chorion.

INTRODUCTION

Studies of the histochemistry and ultrastructure of the uterine epithelium may give information about the effects of the sex hormones at the cellular level. Fraenkel (13) and Corner (10) observed the postovulatory changes in the uterine mucosa in the rabbit and were able to prove that these changes were dependent on the presence of a corpus luteum. Corner and Allen (11) and others (2–4) used this reaction to indicate the presence of progesterone. Nilsson (24) investigated the uterine epithelium in the mouse in order to find ultrastructural indications of the effect of estrogen. The histochemistry of the uterine epithelium has been investigated by Wislocki and Dempsey (29, 30).

It is believed that the postovulatory changes of the uterine mucosa found in most species bring it into a condition favorable for the implantation of the blastocyst. Studies of the ultrastructure of the uterine epithelium during the first days of pregnancy may, therefore, give information about the maternal contribution to the processes involved in implantation. Moreover, that part of the uterine epithelium not removed by the trophoblast continues to function and its secretion products are absorbed by the yolk sac (7, 20) and modified parts of the trophoblast (21).

The object of this investigation has been to examine the ultrastructure of the uterine epithelium under different hormonal influences and the changes of the epithelium during pregnancy.

PREVIOUS OBSERVATIONS ON THE UTERINE EPITHELIUM IN THE RABBIT

Earlier investigations on this subject have been concentrated on the changes in the uterine epithelium before implantation. Duval (12) described the formation of a "symplasma" associated with the disappearance of the cell membranes of the uterine epithelium in the areas of contact with the blastocyst. Fraenkel (13) claimed that these changes in the uterine epithelium were dependent on the presence of a functional corpus luteum. Bouin and Ancel (5) supported this theory by producing multinucleated cells in the uterine epithelium in pseudopregnant rabbits. These observers found numerous mitoses from 24 hours after ovulation and a progressive proliferation and growth of the uterine tissues in the 1st week of pregnancy. At the time when implantation would have occurred, if blastocysts had been present, the superficial epithelium consisted of large multinucleated cells. This epithelium degenerated in the 2nd and 3rd week of pseudopregnancy and on the 20th day the uterine epithelium was found to have the same appearance as in the estrous animal.

MATERIALS AND METHODS

Tissue was obtained from the uterine mucosa of estrous, ovariectomized, pregnant, and pseudopregnant rabbits. The estrous rabbits had been isolated at least 1 month. The tissue from the ovariectomized rabbits was taken approximately 2 months after the operation.

Uterine epithelium from the pregnant rabbits was obtained from following regions: the antimesometrial side, the mesometrial side before implantation, the region between the placental sites and from the non-pregnant horns in unilateral pregnancies. Pseudopregnancy was induced by mating with a vasectomized male and tissue was obtained at the 2nd, 4th, 5th, 7th, 10th, 14th, 18th, and 20th days of pseudopregnancy.

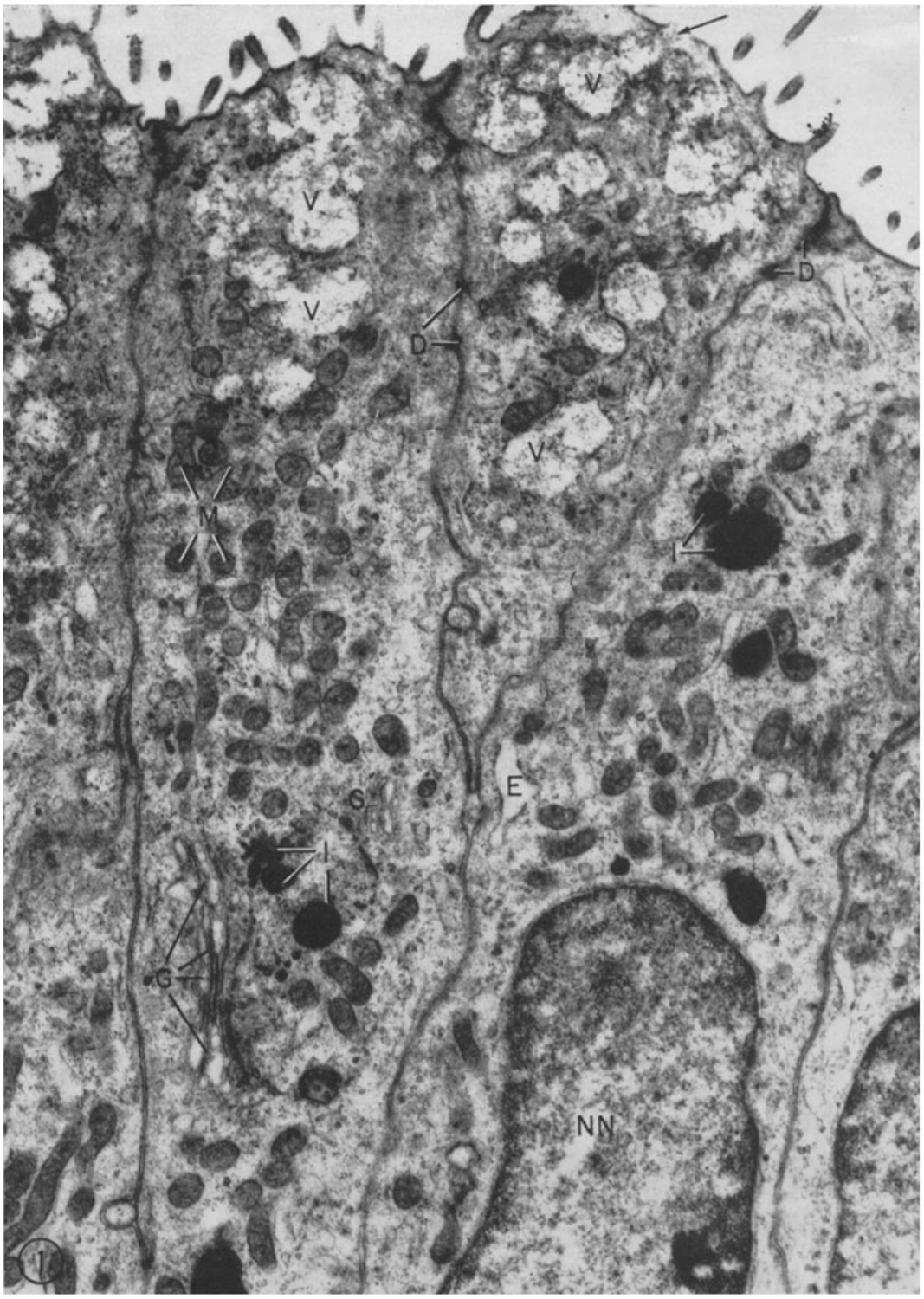
Explanation of Figures

All figures are of uterine epithelium of rabbits.

BM, basement membrane
C, cilia
CF, cytoplasm of fibroblast in uterine stroma
CM, cell membrane
CS, cytoplasm of uterine "symplasma"
D, desmosomes
E, endoplasmic channels
F, foldings of basal membrane of uterine "symplasma"
G, vacuoles and channels of Golgi apparatus
GL, lumen of uterine gland
I, cytoplasmic inclusions
IS, intercellular substance of connective tissue
ISP, intercellular space
M, mitochondria
MF, "myelin figure"
MV, maternal vessel
NA, nucleus of antimesometrial epithelial cell
NC, nucleus of ciliated epithelial cell
NE, nucleus of endothelial cell
ND, nucleus of degenerating epithelial cell
NG, nucleus of glandular epithelial cell
NM, nucleus of multinucleated epithelial cell
NN, nucleus of non-ciliated epithelial cell
NP, nucleus of perivascular cell of connective tissue
SP, cytoplasmic process of uterine "symplasma"
UL, uterine lumen
V, vacuoles containing granular PAS-positive substance (mucus?)

FIGURE 1

Electron micrograph of non-ciliated cells in estrus. The arrow indicates a communication between a luminal vacuole (*V*) containing granular material and the uterine lumen. The mitochondria (*M*) contain electron-opaque bodies. Many inclusions (*I*) are seen. The cell membranes are slightly irregular and desmosomes (*D*) are found. × 10,000.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Tissue for observation in the light microscope was fixed in Bouin's solution, embedded in paraffin, sectioned on a Spencer microtome, and stained with hematoxylin and eosin, by the periodic acid–Schiff (PAS) method, or with methylene blue.

Tissue for electron microscopy was fixed in 1 per cent osmium tetroxide in White's saline (28) for 1 hour. The tissue was washed in distilled water and dehydrated through mixtures of ethyl and butyl alcohol in increasing concentrations to absolute butyl alcohol. After two changes in propylene oxide, the tissue was embedded in English Araldite (26). Ultrathin sections were cut on a Porter-Blum microtome and examined in RCA electron microscopes models EMU 2E or 3C.

OBSERVATIONS

Estrous Rabbits (Figs. 1 and 2, 4 to 6)

A cross-section of the paraffin-embedded uterus showed a stellate lumen. The uterine glands were few and had only shallow extensions into the connective tissue. The uterine epithelium was a cylindrical layer of ciliated and non-ciliated cells. The non-ciliated cells were the most common; they were narrower and their cytoplasm was more eosinophilic than that of the ciliated cells. The cells of the glandular epithelium resembled the non-ciliated cells but were lower. Mitoses were rare. A distinct basement membrane and a brush border were observed in the PAS-stained sections pretreated with saliva. No glycogen was found within the epithelial cells, but PAS-positive granules persisting after the saliva treatment were observed in the luminal part of the non-ciliated cells of the surface epithelium. The same part of the cells stained metachromatically with methylene blue. No reaction was found in the ciliated cells or in the glandular epithelium.

Electron micrographs of the non-ciliated cells (Figs. 1, 4, and 5) showed them to be tall with an ovoid nucleus and one or two peripheral nucleoli. The surface possessed microvilli corresponding in position to the PAS-positive brush border. The cell membranes separating the adjacent cells were slightly undulating with frequent desmosomes. The basement membrane followed the basal cell membrane in its slightly undulating course (Fig. 5). The luminal part of the cell was occupied by large vacuoles containing filiform or granular material (Fig. 1), and in some of the cells com-

FIGURE 2

PAS-reaction on the epithelium in estrus. The non-ciliated cells show a brush border and stained material in the luminal cytoplasm. The ciliated cells show no reaction. × 900.

FIGURE 3

PAS-reaction on the epithelium of an ovariectomized rabbit. The cells are reduced in size, the ciliated type of cell has disappeared, and the staining material in the luminal cytoplasm is absent. × 900.

FIGURE 4

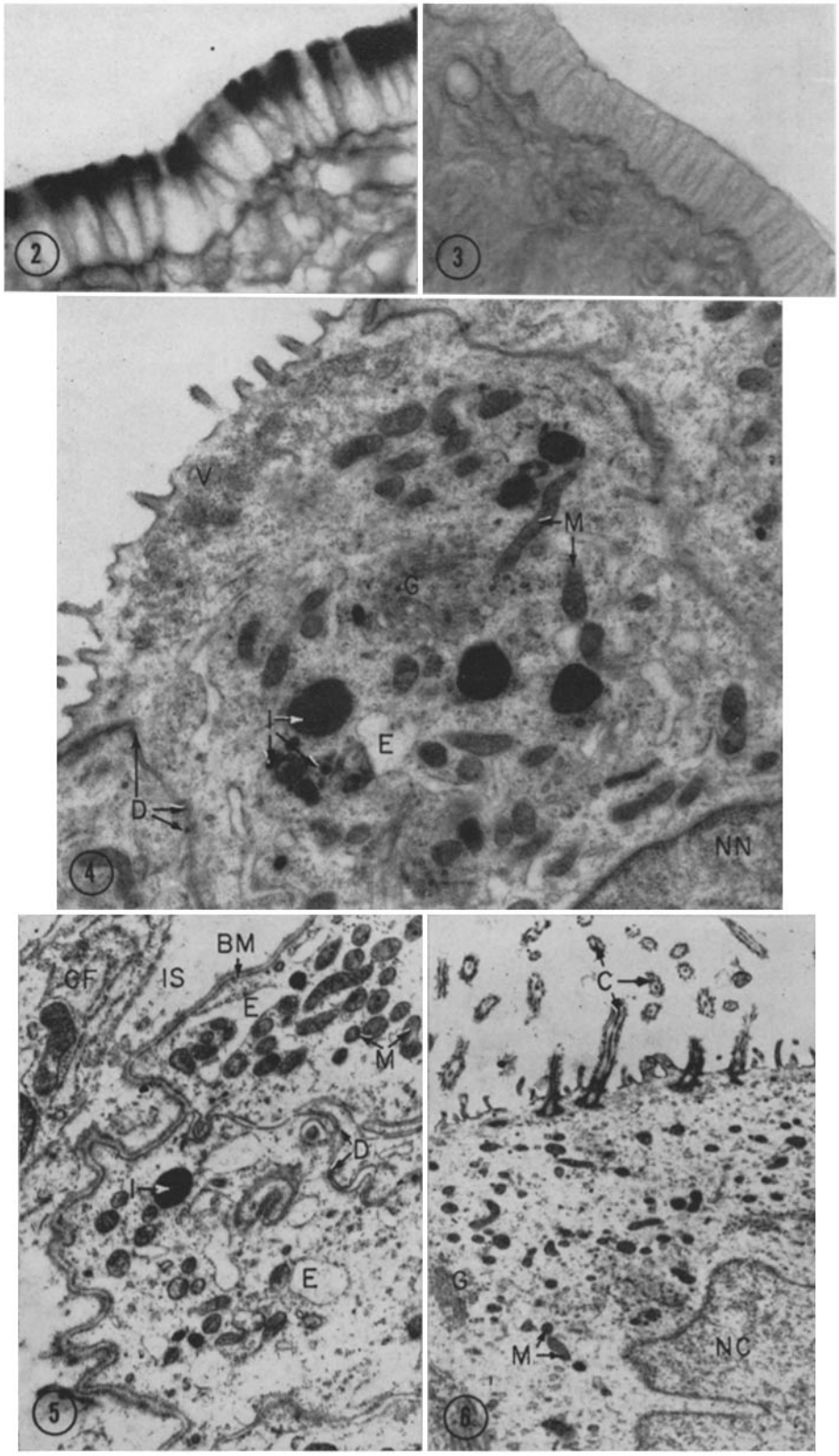
Electron micrograph of epithelial cell in the mouth of a gland in estrus. The luminal vacuoles (*V*) are less developed than in the surface epithelium (Fig. 2), and numerous inclusions (*I*) are found. × 9,100.

FIGURE 5

Electron micrograph of basal part of non-ciliated cells. The basal cell membrane is slightly undulating and a distinct basement membrane (*BM*) is present. ×6,300.

FIGURE 6

Electron micrograph of ciliated cell in estrus. The nucleus (*NC*) has an infolding in the surface, which is a characteristic finding in this type of cell. The mitochondria (*M*) are smaller than those found in the non-ciliated cells. Cilia (*C*) are seen in cross- and longitudinal section. × 7,300.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munications between the vacuoles and the surface were observed. Numerous inclusions of different size and density were found (Figs. 1 and 4). In the mouth of the glands the inclusions were more abundant (Fig. 4) and fewer vacuoles were seen. In the depth of the glands only few inclusions were found in the epithelium. The mitochondria were numerous, elongated, and contained one or two electron-opaque bodies. Near the nucleus there were channels and vacuoles probably representing the Golgi apparatus.

The cytoplasm of the ciliated type of cell (Fig. 6) was less electron-opaque, the nucleus often irregular in shape, and the mitochondria smaller and of more varied shapes. Electron-opaque bodies were also present in the mitochondria of these cells. The cell surface possessed microvilli as well as cilia containing two central and nine peripheral filaments. Inclusions were not seen in this type of cell. The endoplasmic reticulum was poorly developed, but channels and vacuoles of the Golgi apparatus were constant findings.

Ovariectomized Rabbits (Figs. 3 and 7)

The uterus was reduced in size after ovariectomy and the uterine lumen was less complicated in cross-section. The epithelium was considerably lower, the glands were fewer and extended less deeply into the connective tissue. The ciliated type of surface epithelium had disappeared. In PAS-stained sections pretreated with saliva, the basement membrane was observed, but the brush border had disappeared in many places and the PAS-positive material in the luminal part of the cells was no longer present (Fig. 3). The cells revealed a reduction in cytoplasmic basophilia and an absence of metachromatic droplets.

These cells differed in ultrastructure from the non-ciliated cells of the estrous rabbit in that they lacked vacuoles containing granular material and showed a reduction in the number of microvilli (Fig. 7). Inclusions of different size and density were still seen, but they were fewer than in the estrous stage. The number of mitochondria seemed to have been reduced, but they still contained electron-opaque bodies. Small vacuoles and elements of the Golgi apparatus were observed.

Pseudopregnant Rabbits (Figs. 8 to 11)

Forty-eight hours after copulation the uterus was increased in size and numerous mitoses were found, especially in the glands. The mitoses were predominantly in the non-ciliated cells. The brush border was still seen in the PAS-stained sections, but the staining material in the luminal part of the cells was decreased in amount. Electron micrographs of the epithelium at this stage showed that it differed only slightly from that of the estrous phase. The vacuoles in the luminal part of the cells were reduced in size and number.

The proliferation continued in the succeeding days of pseudopregnancy, but the mitoses were less numerous at the end of the 4th day, and only a few were seen on the 5th day. At this stage multinucleated cells were found containing up to a dozen closely packed nuclei. The brush border of this modified uterine epithelium was seen in PAS-stained sections but there was no stained material within the epithelial cells. The ciliated cells were still present but seemed to be reduced in number relative to the non-ciliated cells, which seemed to be involved exclusively in the formation of the multinucleated cells.

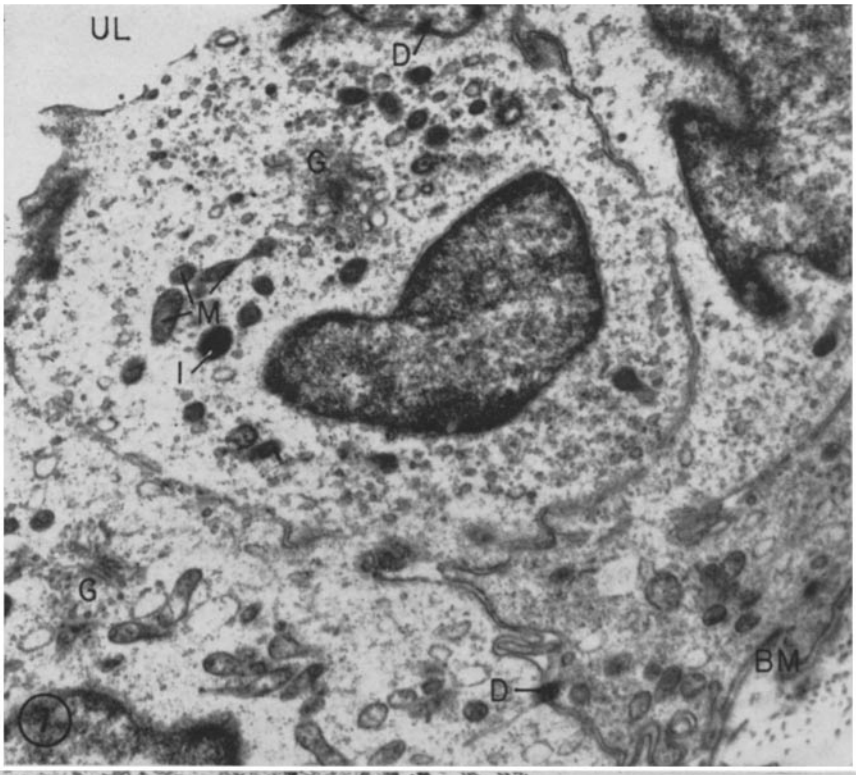
Electron micrographs of the epithelium on the 5th day of pseudopregnancy showed that it contained many multinucleated cells and that the cell membranes persisted (Fig. 8). The nuclei of these cells were irregular in size and shape, the chromatin was concentrated peripherally, and there were no vacuoles in the luminal part of the

FIGURE 7

Electron micrograph of epithelial cell from an ovariectomized rabbit. The number of microvilli is reduced, the nuclei have irregular shapes, and only a few inclusions (*I*) are seen. × 10,000.

FIGURE 8

Electron micrograph of surface epithelium on 5th day of pseudopregnancy. Most of the non-ciliated cells are transformed into cells with many irregular nuclei (*NM*). Ciliated cells are still present. × 5,000.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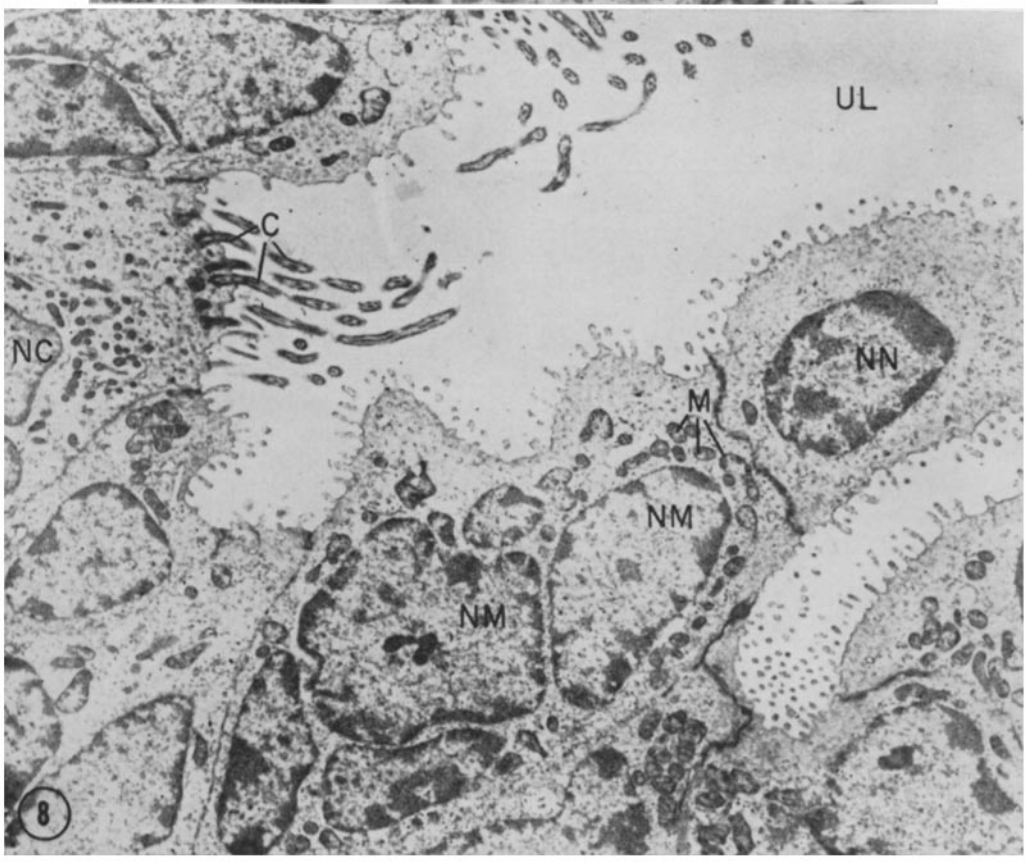
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cytoplasm. Mononuclear cells of the non-ciliated type were still found between the multinucleated cells, and the cells in the deeper part of the glands were unchanged.

By the 7th to the 10th day of pseudopregnancy all the superficial epithelial cells were changed into multinucleated cells (Fig. 9). The cell membranes could still be identified in the electron microscope (Fig. 10). The nuclei were crowded into the center of the cell and were surrounded by a narrow rim of cytoplasm with dilated ergastoplasmic channels. The mitochondria were few and were found in the narrow network of cytoplasm between the dilated channels. In some cases the cell membranes of adjacent cells became highly irregular and intercellular spaces were formed. The cell membranes formed processes simulating microvilli projecting into these spaces.

Degeneration begins in the following days and at the end of the 3rd week of pseudopregnancy the epithelium was restored to its estrous appearance (Fig. 11).

Pregnant Rabbits (Figs. 12 to 19)

The epithelial changes observed in the first 5 days of pregnancy were found to be identical with those described in pseudopregnancy. The first contact between the blastocyst and the uterine epithelium took place during the 7th day of pregnancy at the antimesometrial side of the uterus. By the 6th day the ciliated cells had disappeared and a formation of symplasma was observed at the antimesometrial side in places where the blastocyst was apposed to the epithelium. This seemed to take place by a disappearance of the cell membranes between the multinucleated cells in this region (Fig. 12).

The symplasma was found in all places where the blastocyst lay in contact with the epithelium on the 7th day, and from this stage the formation of a symplasma began at the mesometrial side where the chorio-allantoic placenta is formed later. The nuclei in the symplasma lay centrally and were surrounded by eosinophilic cytoplasm while the rest of the cytoplasm was strongly basophilic. The "symplasmic" change took place not only in the superficial epithelium but also in the glands in the later stages of implantation when these were invaded by the trophoblast. It was still possible in the electron microscope to find parts of cell membranes within the symplasma or rows of vacuoles indicating their former sites (Fig. 14). The nuclei resembled those found in the non-ciliated type of cell in the estrous animal; they were ovoid with one or more peripheral nucleoli. They were arranged in groups between the remains of the cell membranes. There was no sign of degeneration of the nuclei (Fig. 13). The cytoplasm was less electron-opaque in the luminal part of the symplasma and the mitochondria were usually con-

FIGURE 9

Light micrograph of the uterine epithelium on 10th day of pseudopregnancy. The total surface epithelium is transformed into large cells each containing up to a dozen closely packed nuclei. H. and E., × 450.

FIGURE 10

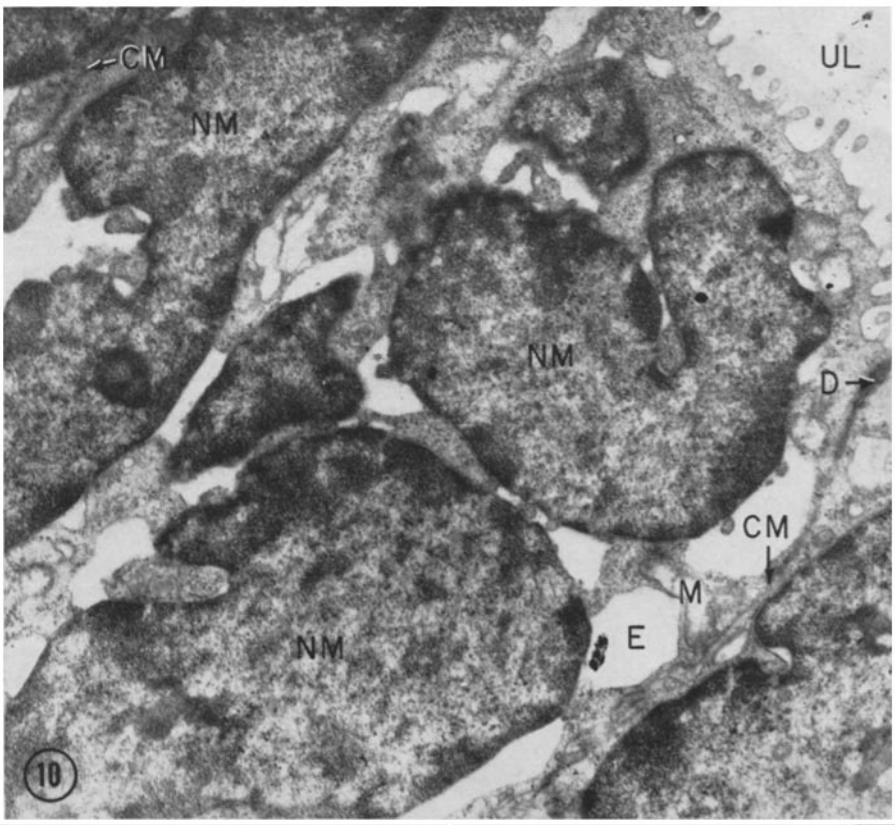
Electron micrograph of a multinucleated cell from 10th day of pseudopregnancy. The nuclei (*NM*) are surrounded by a narrow rim of cytoplasm containing dilated ergastoplasmic channels (*E*). The membranes (*CM*) are present. × 10,000.

FIGURE 11

Light micrograph from late pseudopregnancy. The uterine epithelium is restored to the estrous form and debris, probably derived from the multinucleated cells, is found in the lumen. H. and E., × 250.

FIGURE 12

Light micrograph of "symplasmic" change at the antimesometrial side of uterus on 7th day of pregnancy. The epithelium between the arrows still consists of multinucleated cells, while the rest has been changed into a "symplasma." H. and E., × 250.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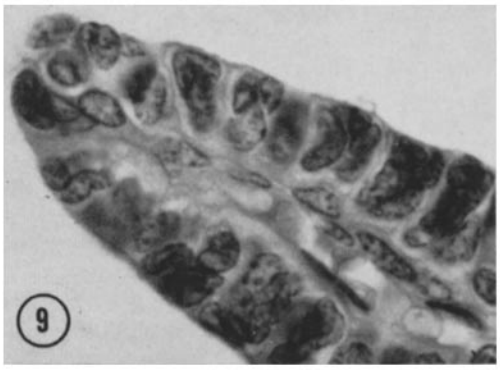
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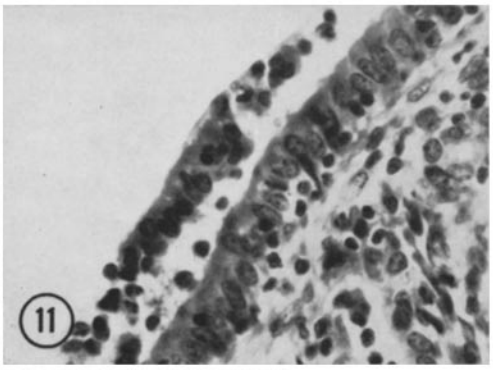
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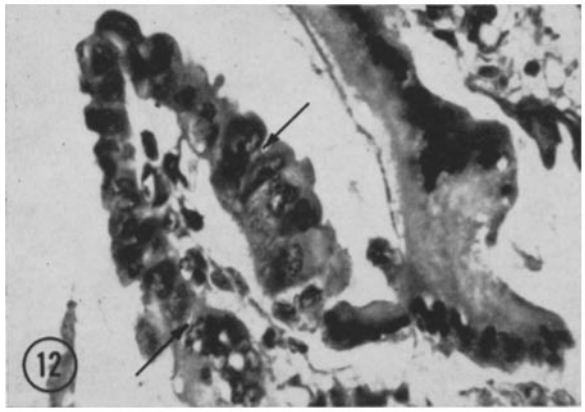
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centrated in the basal part. The surface possessed many microvilli beneath which were found numerous small vacuoles embedded in a homogeneous material of slightly greater density than the underlying cytoplasm. The basal cell membrane was irregular (Fig. 15) and its irregularity increased with the progressive formation of the symplasma (Figs. 13 and 14). In places of direct contact between the epithelium and the trophoblast the outer cell membrane and superficial cytoplasm of the former were extruded as large processes (Fig. 14) obliterating the mouths of the glands. The cytoplasm of these processes appeared less electron-opaque than that of the basal part of the cell; they also contained fewer organelles and inclusions, but localized concentrations of mitochondria were found.

The changes in the uterine epithelium on the mesometrial side during implantation and the formation of the chorio-allantoic placenta have previously been reported (19). During the 7th and 8th days of pregnancy the temporary yolk-sac placenta is formed on the antimesometrial side. The rôle of the uterine epithelium in the formation of this structure will be discussed in another paper (20). The temporary non-vascular yolk-sac placenta degenerates during the 11th and 12th days and the uterine epithelium on the antimesometrial side is restored. At this stage this epithelium consisted of simple columnar cells, each with one nucleus. The cytoplasm was strongly basophilic and there was a PAS-positive brush border. In the electron microscope the cells showed a richly developed ergastoplasm with dilated channels (Fig. 16).

The uterine epithelium in the non-pregnant horn of unilateral pregnancies showed changes during the 1st week which were similar to those seen in pseudopregnancy. Multinucleated cells were formed but no formation of symplasma was seen. The multinucleated cells persisted in the non-pregnant horn until the last week of pregnancy when degeneration was found in many places, similar to that occurring in the 2nd week of pseudopregnancy. The cells of the glandular epithelium in the non-pregnant horn became very basophilic in the 2nd and 3rd weeks, and in the electron microscope these cells were found to be very rich in ergastoplasm, resembling the cells on the antimesometrial side (Fig. 17).

The uterine epithelium between the placental sites showed changes similar to those found in the non-pregnant horn in unilateral pregnancy. The underlying tissue, however, showed a decidual reaction but this did not seem to affect the epithelium. During the last 2 weeks of pregnancy the degeneration in this epithelium increased and was accompanied by the appearance of PAS-positive bodies (Fig. 18). In the electron microscope these bodies were found to be intracellular and resembled "myelin figures" (Fig. 19).

DISCUSSION

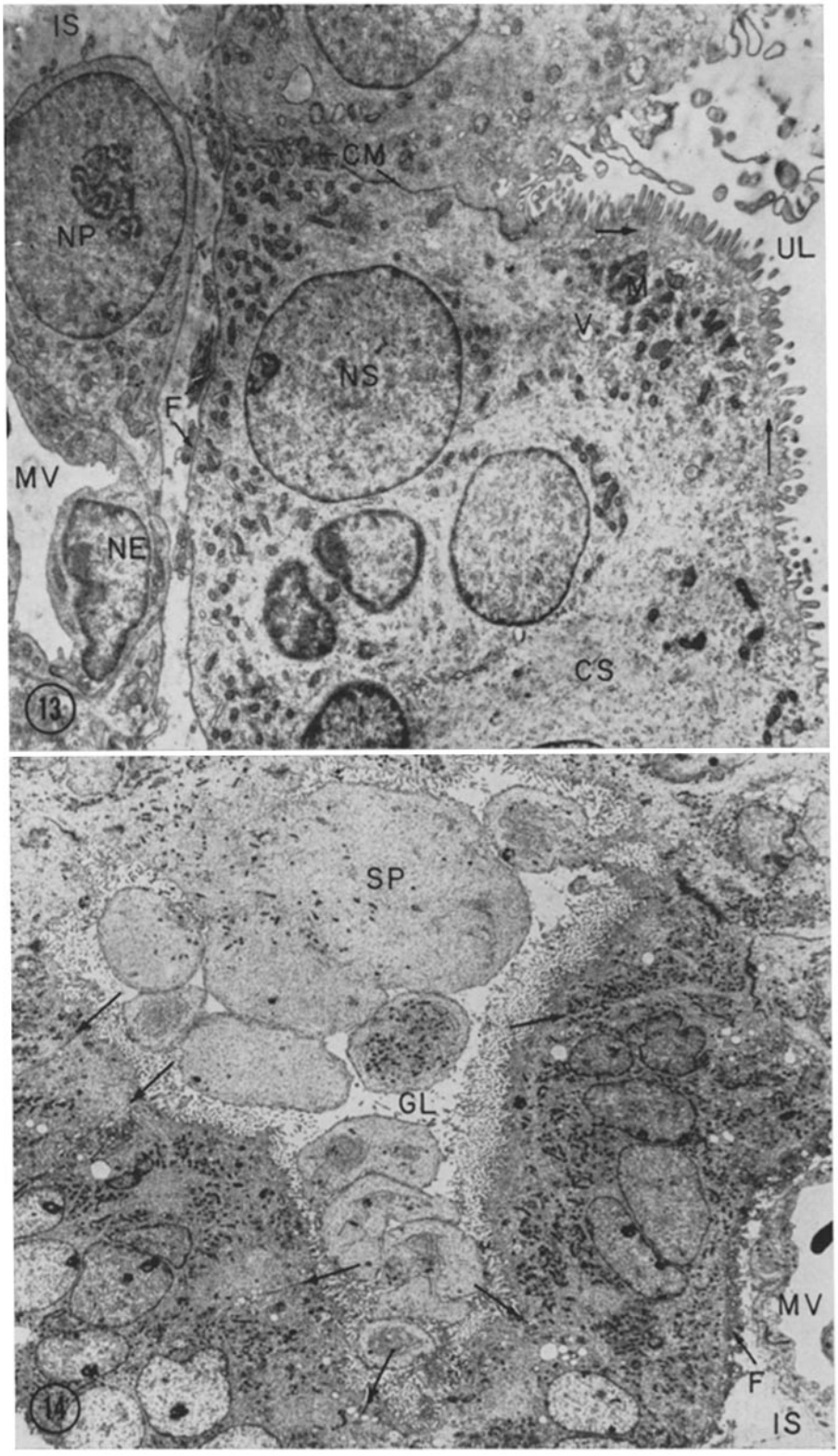
Both a ciliated and a non-ciliated type of cell in the uterine epithelium of the rabbit have been described in this paper. Ciliated cells are known to exist in the human uterus (14), but this type of cell was not described by Cartier and Moricard (8) in their paper on the ultrastructure of the uterine epithelium. Nilsson (24) also did not mention ciliated cells in his paper on the uterine epithelium of the mouse. This author found electron-opaque bodies in the mitochondria, while Cartier and Moricard did not observe such

FIGURE 13

Electron micrograph of two multinucleated cells undergoing "symplasmic" change on the 8th day of pregnancy. The nuclei (*NS*) are situated in the basal part of the cytoplasm. The microvilli of the upper cell are very irregular. The superficial cytoplasm contains vacuoles found embedded in a homogeneous material (between the arrows). A cell membrane (*CM*) is still present between the cells. The plasma membrane facing the connective tissue is folded (*F*). × 5,000.

FIGURE 14

Electron micrograph of an uterine gland on the 9th day of pregnancy. The lumen (*GL*) is almost obliterated by large cytoplasmic processes (*SP*) from the uterine symplasma. The arrows indicate the positions of the former cell membranes. The folding (*F*) of the basal cell membrane is more developed than in Fig. 13. × 2,000.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granules in the mitochondria of the human uterine epithelium. The significance of the mitochondrial bodies is unknown; it has been suggested, however, that they might be associated with salt and water metabolism (27). These bodies may provide practical criteria in differentiating maternal from fetal tissues in electron microscopic studies of the implantation process, as mitochondrial bodies were not found in the trophoblastic epithelium. Glycogen was not found within the epithelial cells, in confirmation of the observation by Chipman (9).

The characteristic microvilli and luminal vacuoles were also found in the human (8) and mouse (14) epithelium, but the large vacuoles containing granular, PAS-positive material were not described. Histochemical and electron microscopic evidence suggest that these vacuoles contain mucus. They disappear after ovariectomy and a few days after ovulation, facts which might indicate that the presence of this material is regulated by estrogen. The effect of ovariectomy is seen not only in the reduction in size of cells but also in the loss of their "active appearance"; the microvilli are less pronounced, the luminal vacuoles few, and the granular, PAS-positive material is missing. Gilbert (15) found an increase of basal fat droplets in the uterine epithelium of the ovariectomized rabbit treated with estradiol and progesterone and suggested that the number of droplets was regulated by progesterone. The investigation reported in this paper does not include staining of tissue for fat, but fat droplets were not visible in the tissue fixed for electron microscopy, so the observations have not supported the theory of Gilbert (15).

The changes in the uterine epithelium before implantation seem to be induced by two different factors: a hormonal influence causing the formation of multinucleated cells, and a local (chemical?) effect produced by the blastocyst causing the formation of the "symplasma." In favor of this theory is the fact that the formation of multinucleated cells is seen in all cases where the epithelium is under progestational influence (in the epithelium of pregnancy, pseudopregnancy and in the non-pregnant horn in unilateral pregnancy), while the symplasma is formed only where the blastocyst is in contact with the uterine epithelium. The symplasmic change preceding the implantation seems to be a general feature in all species and this change is always limited to the areas of the epithelium in contact with the blastocyst (17, 18). It is also seen in the epitheliochorial placenta of the pig in the early stages, but later the cellular appearance of the epithelium is restored (1). That the formation of the symplasma is not a simple degeneration has been shown in this paper and in the earlier paper on the implantation process (19). It is, therefore, reasonable to conclude that this change plays an important rôle in the implantation process.

The formation of multinucleated cells has not been described in any other species, as far as the author is aware. Corner and Allen (11) showed that the progestational preparation was necessary for the *in vivo* implantation of the blastocyst in the rabbit, and it seems likely that the formation of the multinucleated cells is a preliminary stage in the epithelial modification which at the actual implantation site leads to the formation of a true syncytium. Glenister (16) claims that he has been

FIGURE 15

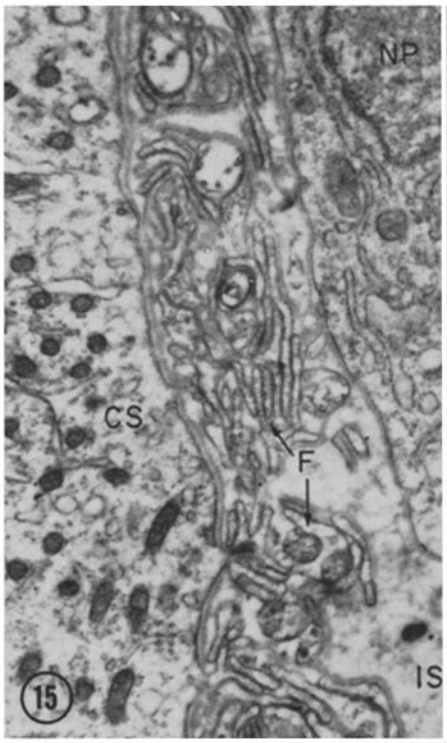
Electron micrograph of the basal cell membrane of the uterine symplasma on the 9th day of pregnancy. A part of a perivascular cell is seen at the right. × 19,200.

FIGURE 16

Electron micrograph of the epithelium of the antimesometrial side of uterus on the 16th day of pregnancy. Most of the cytoplasm is occupied by dilated ergastoplasmic channels (*E*). A Golgi apparatus and numerous small granules are present in the luminal cytoplasm together with many mitochondria (*M*). × 9,600.

FIGURE 17

Electron micrograph of parts of two glandular cells from the non-pregnant horn in a unilateral pregnancy. The cytoplasm contains closely packed ergastoplasmic channels (*E*) between which inclusions (*I*) and mitochondria (*M*) are found. × 24,000.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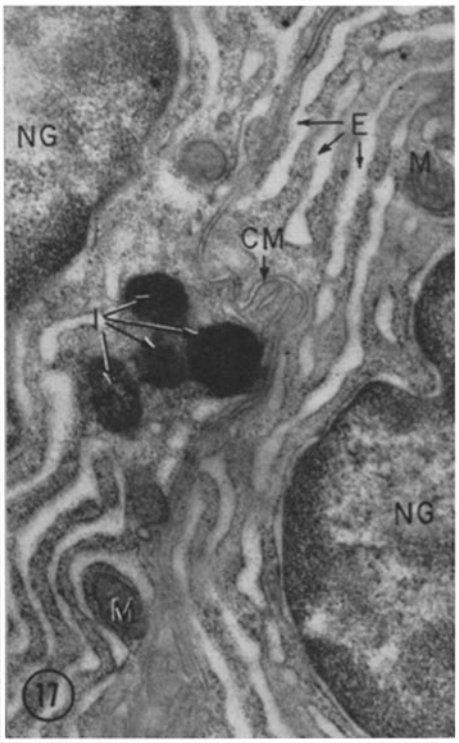
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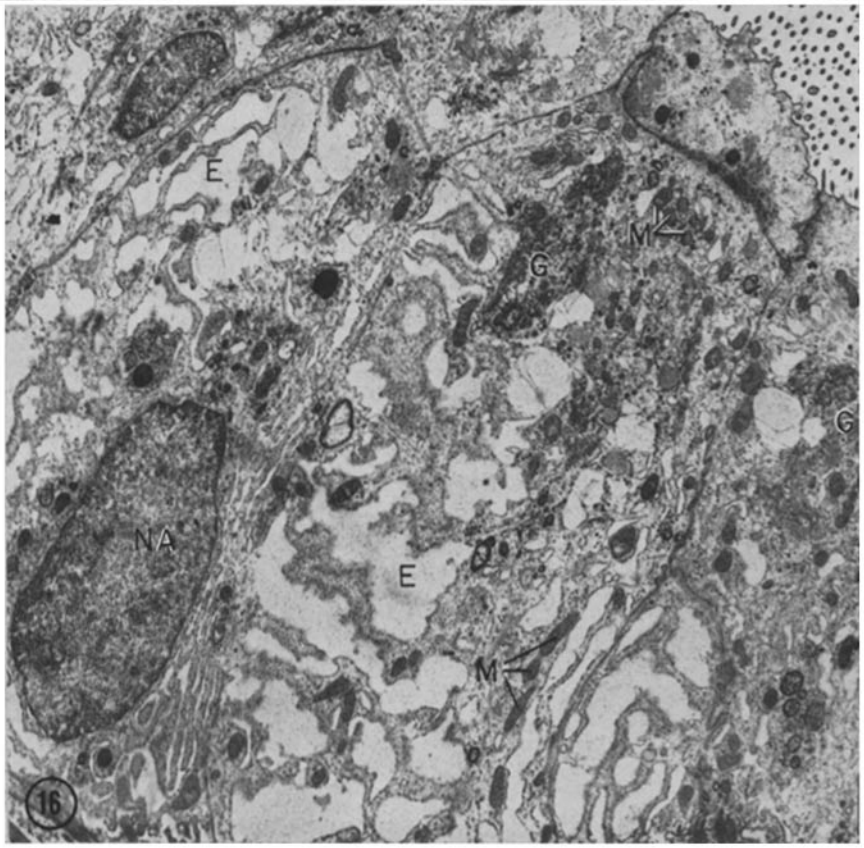
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able to show the implantation of the rabbit blastocyst in tissue cultures of uterine epithelium in non-progestational (estrous and virginal) phases. He also showed that the blastocysts invaded the connective tissue in the absence of the uterine epithelium. These experiments do not truly imitate the interactions of the blastocyst and the uterine epithelium in implantation *in vivo*, where a symplasmic change in the epithelium always occurs as a result of a combined hormonal and chemical preparation. The phenomenon observed could be called more correctly an ingrowth of trophoblastic tissue into a non-specific tissue *in vitro*. True implantation is a far more complicated process, as indicated by the electron microscopic studies (19).

The complex infolding of the basal cell membrane and the basement membrane seems to be associated with the formation of the symplasma. The foldings are not seen in the pseudopregnant uterus nor in the non-pregnant horn in unilateral pregnancy. Neither is it seen in relation to isolated cells that do not take part in the symplasma (Fig. 6 in reference 19). The significance of this folding is not known. The basal cell membrane of the epithelium in the distal convoluted tube in the kidney (25), in the choroid plexus (23), and in the secretory duct of the parotid gland (22) also shows complicated foldings which, however, are different in appearance. The membranes in these cells are rather inflections into the basal part of the cells, while the foldings in the uterine symplasma are processes extending into the connective tissue (Fig. 15). In the former cells the infoldings are believed to be associated with fluid transport. Fluid exchanges between the uterine epithelium and blastocyst are probable and may be func-

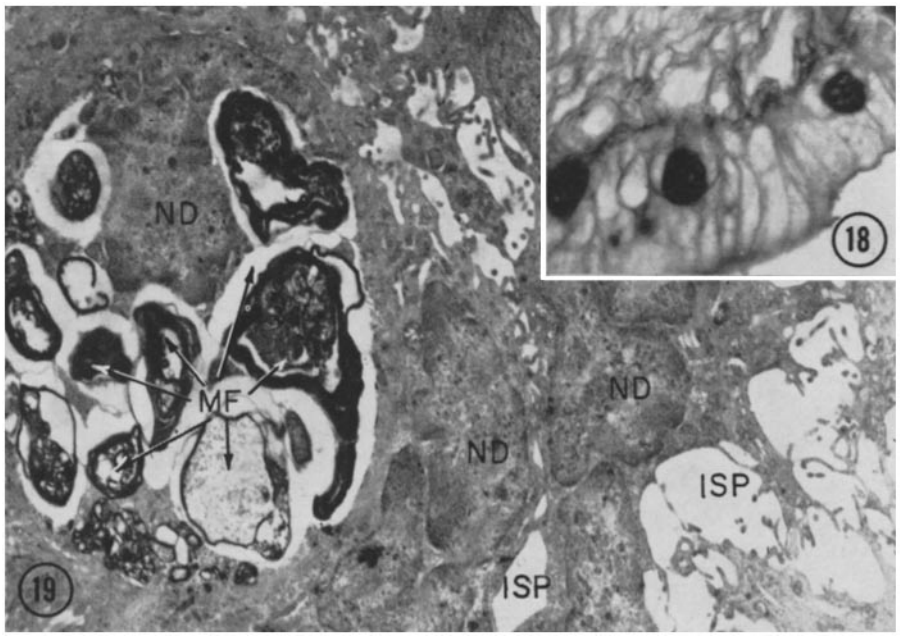

FIGURE 18

PAS-positive bodies in the epithelium between the placental sites. × 900.

FIGURE 19

Electron micrograph of epithelium between placental sites. The cytoplasm shows increased density, perhaps an indication of degeneration, and in one of the cells a "myelin figure" is formed. Irregular spaces (*ISP*) are found between the cells and the cell membranes are drawn out in microvillus-like projections. × 8,000.

tionally correlated with the foldings of the plasma membrane of the uterine symplasma.

The active glandular and superficial epithelium of the remaining uterine mucosa during pregnancy is interesting, because its secretion products are at the continued disposal of the fetus through the inverted yolk sac (7, 20) and the paraplacental chorion (21).

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