

AN ELECTRON MICROSCOPE STUDY OF THE GLAND CELLS OF THE MINK ENDOMETRIUM

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ABSTRACT

Portions of mink endometrium in delayed implantation, early postimplantation, and pseudo pregnancy were fixed in buffered osmium tetroxide with sucrose, or potassium permanganate. After rapid dehydration the portions of endometrium were embedded in either methacrylate or epoxy resin. Examination of the cells from the body of the glands of the endometrium of delayed implantation revealed the presence of prominent terminal bars, numerous secretion granules, and membrane discs in the apical region of the cell. In the supranuclear and infranuclear regions, mildly dilated cisternae of the endoplasmic reticulum were present, and in many cells unusually large mitochondria were seen. Numerous changes were noted in the gland cells of the post implantation stage. The endoplasmic reticulum in the basal region was extensively dilated, and the nuclei were situated more centrally. Giant mitochondria were no longer present. The large secretion granules were not present, but smaller granules were seen, especially in the Golgi region. Some of the Golgi cisternae were dilated and the pattern of parallel membranes was consequently less distinct. It is suggested that gland cells in the postimplantation and pseudopregnancy stages exhibit evidence of greater secretory activity than those in the delayed implantation stage.

Studies with the electron microscope of the human endometrial gland cells during the menstrual cycle have shown that the high glycogen content of these cells in the secretory phase is situated primarily basally, and that large mitochondria are associated with this region of the cell (21, 24, 28, 36, 40). The nature of the secretory process has not been so clearly delineated. Nilsson (29-34) has shown that the morphology of the free surface of the endometrial epithelium of the mouse undergoes variation in structure, especially in the length of microvilli, in response to variations in estrogen level. He reports similar variations in the luminal epithelium of the human endometrium (35-37) during the menstrual cycle. A number of observations on the endometrium of pregnancy

of various species have been made, primarily in the course of studies of placentation (8, 9, 11, 25, 42). Of the earlier studies, the report of secretion granules and extensive endoplasmic reticulum in the uterine epithelium of the pig (9), an animal with epithelio-chorial type of chorio-allantoic placenta, is of particular interest. Recently, Larsen (25) studied the endometrium of estrous, ovariectomized, pseudopregnant, and pregnant rabbits. He reported the formation of multinucleate giant cells with enlarged cisternae of the endoplasmic reticulum in pseudopregnant animals, and the formation of a syncytium from the uterine epithelium (symplasma) at the onset of implantation.

In the study reported here, use has been made

of the phenomenon of delayed implantation, which permits the separation of the time of fertilization and ovum transport through the oviduct from the time of implantation, and permits us to observe the changes in the endometrium from conditions in which the blastocysts are maintained, but do not implant, to those in which implantation and development proceed. Our attention was focused on the gland cells, since preliminary observations indicated that these cells, which are particularly abundant in carnivores, underwent greater alteration at implantation than did the luminal epithelial cells.

Mink exhibit a type of delayed implantation which is unique. Between mating and implantation, there is an interval in which the blastocyst remains unattached within the uterus, and during which successive matings may take place (14). The length of the period of delayed implantation depends on how early in the season the female breeds, since implantation tends to occur in all individuals in a given locality at approximately the same time (13, 14, 22). During the delayed implantation period, the mink endometrium consists of a series of longitudinal folds, usually four to seven in number, which are richly glandular. The individual glands within these folds can be roughly divided into a short junctional or mouth region, an intermediate region which constitutes the main body of the gland, and a dilated basal portion (12). It is the cells of the intermediate portion or body of the gland which are the predominant cell type, and which constitute the subject of this study.

MATERIALS AND METHODS

The mink were bred in Swarthmore, Pennsylvania, and flown to Houston, Texas, 1 to several days before necropsy. The uteri of these animals were removed

under ether anesthesia and examined for implantation sites. If no sites were grossly visible, the cranial portion of one horn was flushed with saline to determine whether or not blastocysts were present. Samples of endometrium were collected from a total of 21 uteri: 10 from the period of delayed implantation, 7 from various stages after implantation, and 4 from pseudopregnant animals.

Small portions of the endometrium from unflushed areas of the uterus or between implantation sites were placed in cold buffered osmium tetroxide plus sucrose (5) or cold 1.2 per cent potassium permanganate (26) in 0.9 per cent sodium chloride. Portions of 5 of the endometria were dehydrated in alcohol and embedded in methacrylate. Pieces of the other 16 endometria were dehydrated rapidly in cold ethyl alcohol, placed in propylene oxide, then embedded in Araldite 502 epoxy resin. Sections from the blocks of osmium tetroxide-fixed material were stained by a modified lead hydroxide method (6).

The orientation of the tissue in the sections and the staging of secretory activity were facilitated by examination of thick sections with the phase microscope and by staining of similar sections with the periodic acid-Schiff technique.

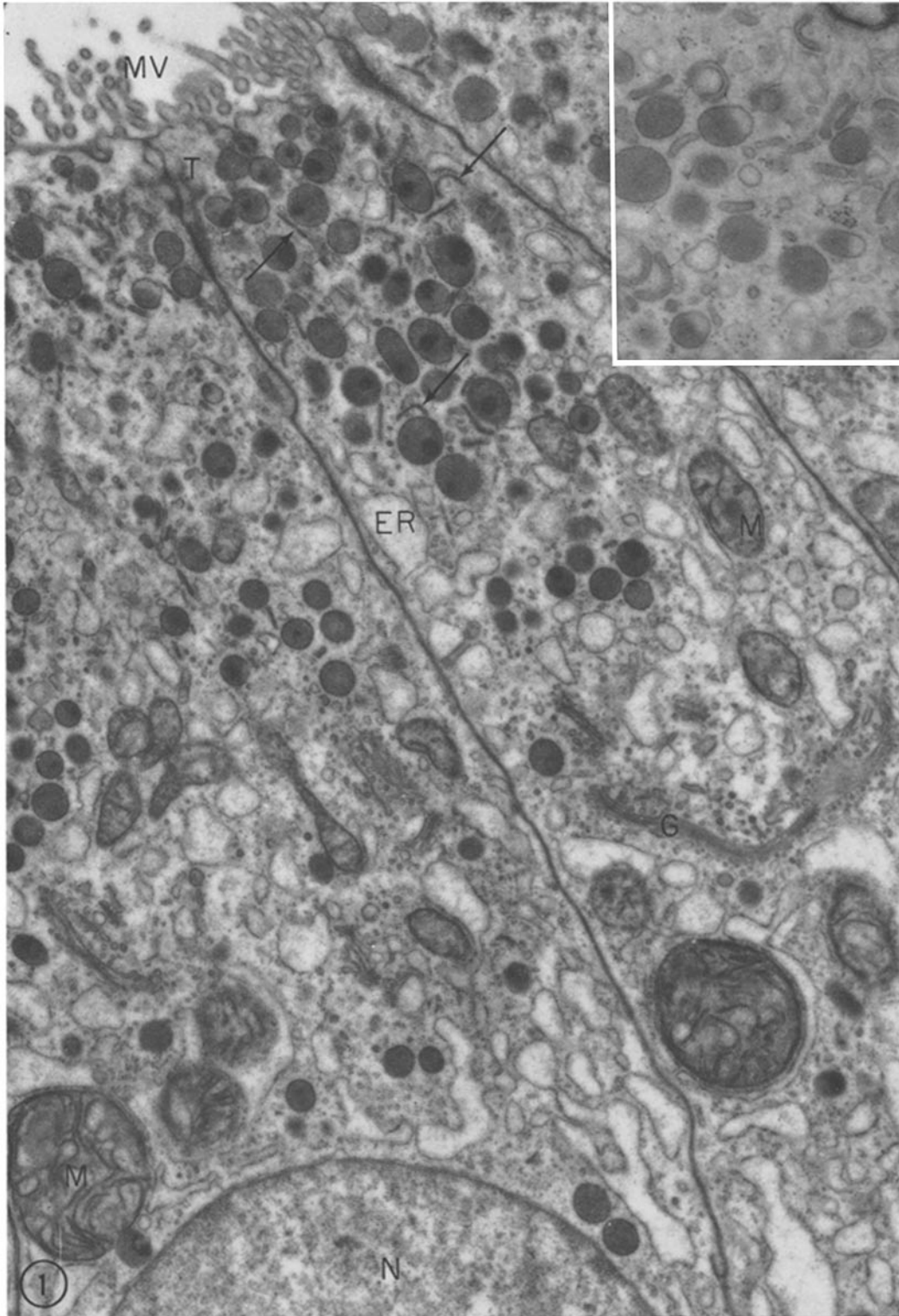
OBSERVATIONS

Gland Cells in the Period of Delayed Implantation

SURFACE RELATIONS: Regular microvilli are present on the otherwise flat luminal surface of the gland cells (Fig. 1). Just beneath the surface, at the lateral margins of the cell, are prominent terminal bars. These bars are composed of an amorphous, moderately dense material which extends in an irregular fashion along the adjacent cell membranes and into the cytoplasm (Figs. 2 and 3). In the region of this amorphous material, and sometimes extending apically, the membranes of the apposed cells are relatively close together.

FIGURE 1 This is a section of the apical, Golgi, and supranuclear regions of an endometrial gland cell of a mink in delayed implantation. Note that there are numerous secretion granules, and that many of these granules have a secondary dense body in addition to a limiting membrane. The arrows point to membrane discs. Note also that the mitochondria (*M*) in the supranuclear region are large and spheroidal, with apparently lamelliform cristae. The tissue in this and all subsequent figures was fixed in buffered osmium tetroxide plus sucrose, embedded in epoxy resin, and stained with lead hydroxide. *ER*, endoplasmic reticulum; *G*, Golgi region; *MV*, microvilli; *N*, nucleus; *T*, terminal bar region. $\times 17,000$.

The insert shows a number of secretion granules and membrane discs at a higher magnification. Note the cupped shape of some of the discs, the circular outline of one of the cupped discs, and the presence of areas of lesser density in some of the granules. $\times 30,000$.



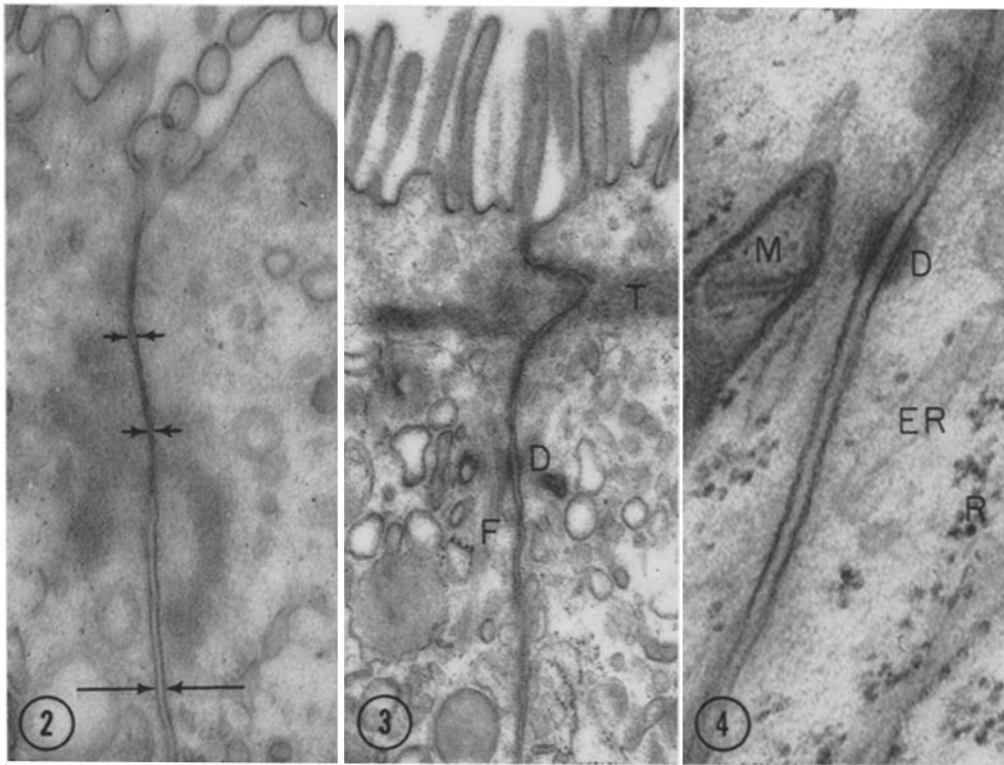


FIGURE 2 The dense amorphous material forming the terminal bar extends irregularly into the cytoplasm in the center of the picture. Note the close but somewhat irregular proximity of the cell membranes in the terminal bar region (small arrows), and the relatively greater distance between the cell membranes below the terminal bar (large arrows). $\times 54,000$.

FIGURE 3 The terminal bar material (*T*) extends laterally some distance into the cells. Note that at the desmosome (*D*) the cell membranes are an appreciable distance apart, and that fibrils (*F*) are present. $\times 31,500$.

FIGURE 4 A small desmosome (*D*) showing strict parallelism of the cell membranes within the desmosome, and an absence of constriction in this area. *ER*, endoplasmic reticulum; *M*, mitochondrion; *R*, ribosomes. $\times 104,000$.

However, the spacing between the cell membranes is uneven, and strict parallelism is not observed throughout the terminal bar area. The distance between the cell membranes in this position is considerably less than the corresponding distance in the typical desmosomes present farther down along the cell membranes. In occasional favorable sections of both osmium- and permanganate-fixed material, there appears to be actual fusion and consequent formation of "tight junctions." In most instances, however, the unit membranes

are not resolved and the shortest distance between the two dense lines at the position of the two cell membranes is roughly 30 per cent of the minimum distance in other regions of apposition. At irregular intervals from the basement membrane to the terminal bar region, desmosomes are found. These desmosomes have a discrete disc of dense material, associated tonofibrils, and a constant distance between apposing membranes, such that parallelism is maintained throughout the length of the desmosome (Fig. 4).

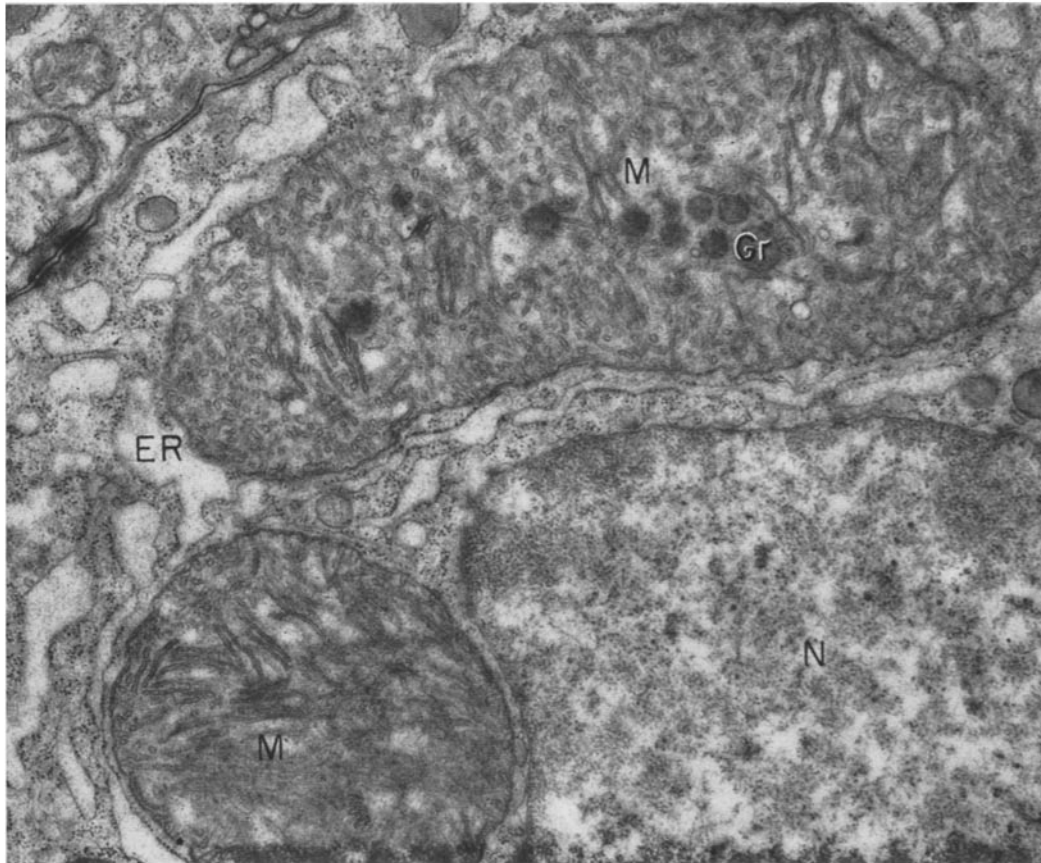


FIGURE 5 Two of the unusually large mitochondria (*M*) frequently seen in the infranuclear region of gland cells in the delayed implantation period. Note that the majority of the cristae are villiform. There are two desmosomes in the upper left corner. *ER*, endoplasmic reticulum; *Gr*, intramitochondrial granule; *N*, nucleus. $\times 26,000$.

Some interdigitation of cell processes is present in an irregular form, but such interdigitations are not a conspicuous feature of this cell type.

The basal cell membrane of the gland cell is smooth, with only minor indentations. Apposed to this membrane is a distinct and continuous basement membrane, which is markedly thinner than the basement membrane of the luminal epithelium. The smooth contour of the gland is occasionally indented by a capillary. Non-myelinated nerve fibers are also in close association with the glands, but, in all instances, the basement membrane plus an interval, in which collagen fibers are usually present, separates such structures from the gland cell.

INTERNAL STRUCTURE: Characteristically, the nuclei of the gland cells are somewhat below the mid line, have few annuli in their nuclear envelopes, and contain single, prominent nucleoli. The presence of an extensive Golgi zone above the nucleus and somewhat removed from it divides the cell into roughly four regions: infranuclear, supranuclear, Golgi zone, and apical.

In the infranuclear cytoplasm are extensive dilated cisternae of the endoplasmic reticulum. Numerous ribosomes are present both in the cytoplasm and in irregular association with the membranes of the endoplasmic reticulum. Many of the mitochondria found in the infranuclear region are of normal size, but unusually large mito-

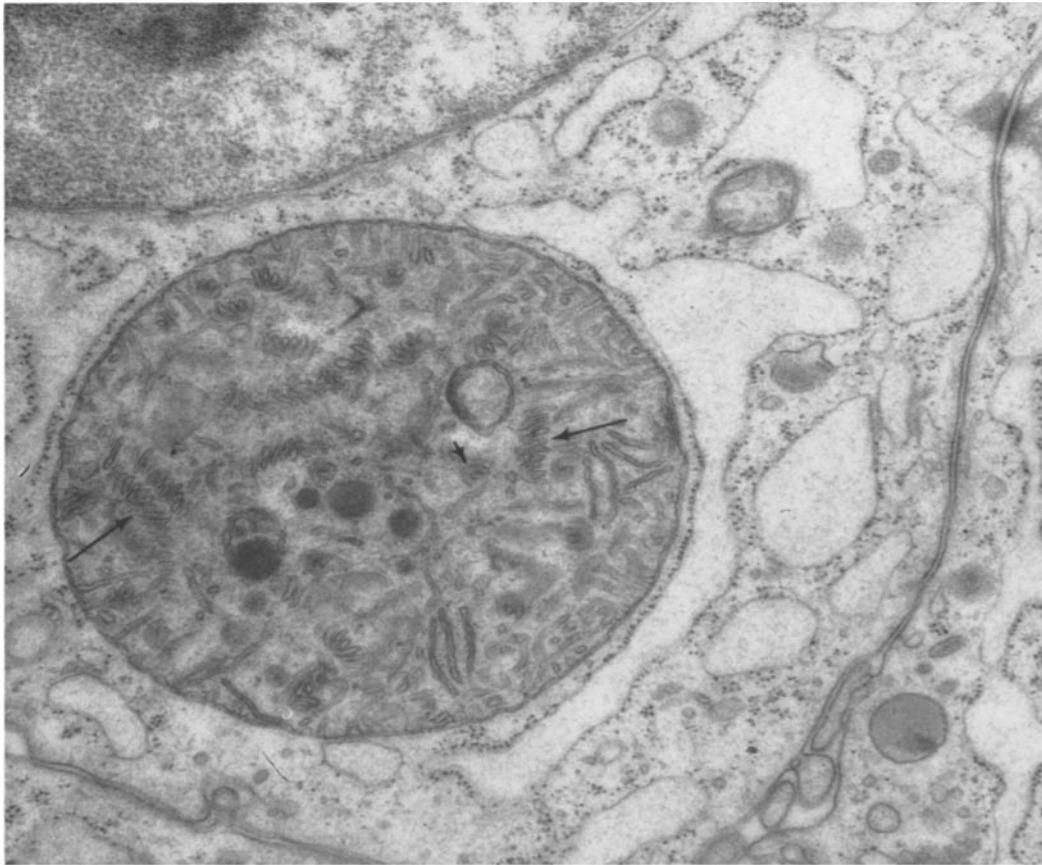


FIGURE 6 In this large mitochondrion the spiral nature of some of the cristae is seen. The large arrows show typical longitudinal sections of spiral cristae; the small arrow shows a cross-section. Other cross sections and parasagittal sections of spiral cristae can be seen in both this mitochondrion and the mitochondria in Figure 5. Note the manner in which the endoplasmic reticulum partially surrounds the mitochondrion. $\times 46,000$.

chondria are frequently present in this region. These large mitochondria are spheroidal in shape, with a diameter three to four times as large as that of the smaller mitochondria within the cell. Occasionally, extremely large mitochondria with a diameter of 2 to 3 μ or more are found in this area (Fig. 5). The cristae of these unusually large mitochondria are most commonly simple villiform, but lamelliform cristae and spiral villiform types are also encountered. Single and double spiral cristae are present only in the larger mitochondria (Fig. 6). One or more granules are present within most of these mitochondria,

usually in the central region. Such granules reach a size of 0.1 to 0.2 μ .

The supranuclear cytoplasm is similar in constituents to the infranuclear cytoplasm, with the exception that secretion granules are often present in this region.

The membranes and vesicles of the Golgi complex are found in a distinct zone some distance above the nucleus. Parallel membranes of the Golgi cisternae are numerous, and are typically arrayed in circular patterns in cross-sections of individual cells and in cylindrical or cup-shaped patterns in sagittal sections. In general, the cisternae tend to

form the periphery of a squat cylinder about two-thirds of the width of the cell, with vesicles, secretion granules, and other substances present within the Golgi zone. Although the secretion granules in the Golgi zone are sometimes quite small, more often only larger secretion granules are present.

The apical region of the cell is markedly different from the infra- and supranuclear areas (Fig. 1). The mitochondria are smaller in diameter, and are more elongated. A few dilated elements of the endoplasmic reticulum are present, but the cisternae are smaller and tend to be restricted to the more basal portion of this region. Characteristic of the apical region is the presence of secretion granules, which vary from 0.2 to 0.5 μ in diameter and are relatively numerous in many of the cells but sparse in others. When only a few granules are present, they tend to be restricted to the extreme apical cytoplasm. Many of the secretion granules have a moderately dense, uniformly granular interior, surrounded by a thin but generally distinct membrane. In some instances the limiting membranes of these granules are irregular, and in permanganate preparations the limiting membranes are usually incomplete. Frequently, an area of secondary density is present within the granules. Less commonly, areas of lesser density are present at one pole of the granules. A few granules appear ellipsoidal or flattened rather than spherical in section.

In the apical region of many of the cells are numerous short elliptical profiles of membranes. These membranes take the form of a flattened vesicle or disc, since they are closed structures with greater width than depth, and may occasionally show circular or cup-shaped profiles. In a number of instances, a substance similar in density to that of the secretion granules is found within these membrane discs. The total area of membrane involved in the individual discs does not appear to exceed the area of membrane enclosing the larger secretion granules.

A few small vesicles are also found in the apical region of the cytoplasm. Sections of this region often include an eccentrically placed centriole.

Changes in Gland Cells Accompanying Implantation

Gland cells late in the period of delayed implantation, in postimplantation, or in pseudo-

pregnancy are markedly different in structure from those of the earlier period (Fig. 7). The microvilli are more numerous and frequently more irregular, and are closely associated with the numerous secretion droplets usually present in the lumina of these glands. The lateral and basal relationships of the cell membranes remain similar, except that in many instances there is an intraepithelial intercellular space near the basal region of the cells between their lateral margins. These spaces are occasionally dilated and in some instances occupy a considerable area. However, in better preparations, they are not extensive, indicating that the more expanded intercellular spaces may have formed during preservation of the tissue.

The infranuclear zone of the gland cells in the postimplantation stage is characterized by extreme dilation of the cisternae of the endoplasmic reticulum (Fig. 8). This dilation is not so marked in the late delayed implantation stage as in postimplantation stage, in which the areas of the cytoplasm may be restricted to thin strands between the cisternae. The cisternae contain a uniformly distributed, fine granular material. Numerous ribosomes are present in clusters within the cytoplasm and in irregular association with the cisternae. In contrast to the condition in the previous stage, the mitochondria of this region are not unusually large, and tend to be elongated rather than spheroidal, and to have lamelliform cristae. Frequently, a number of droplets which appear lipoidal in nature are present within the infranuclear zone in clusters near the basal cell membrane.

The supranuclear zone is similar to the infranuclear zone, except for the absence of lipid material and a greater abundance of cytoplasm.

Within the Golgi region, some of the cisternae are dilated. Consequently, the membranes are not in parallel arrays, and the zone, as a whole, is less distinct in shape than in the previous stage (Fig. 9). The dilated Golgi cisternae contain neither the fine granulation present in the endoplasmic reticulum, nor other discernible particulate matter. Dilated cisternae of the endoplasmic reticulum are in close association with this region, and small secretion granules are present in the cytoplasm of this region.

The apical region of the cell is relatively devoid of secretion granules, when compared with cells of previous stages, and membrane discs are rare.

The secretion granules that are present are mostly small and lack areas of differential density. Some cisternae of the endoplasmic reticulum extend well into the apical region. Mitochondria are more numerous in this than in the other regions.

DISCUSSION

Terminal bars frequently have been considered similar to desmosomes, differing from the latter structures primarily in shape and extent (19). Recently, however, Farquhar and Palade (16, 17) have restudied the problem of close association of membranes on the lateral surface, and have added the concept of the "tight junction" and associated "intermediate junction" to that of the desmosome. In addition, they point out that the terminal bars may be formed from different contributions of these elements in different cells.

In the mink endometrial gland, cell membranes are more closely apposed in the terminal bar region than in the desmosomes. Furthermore, the space between the cell membranes is less uniform in the terminal bar region, even in sections normal to the plane of the basement membrane, than it is in the shorter, more discrete desmosome. In the majority of instances, however, fusion of the outer units of the unit membrane could not be clearly demonstrated, nor could regions of strict parallelism be seen. The regions of close apposition within the terminal bar region for which fusion could not be demonstrated may actually constitute unresolved tight junctions, although "intermediate junctions" are lacking. It seems equally possible that many of the regions of close apposition are just that, namely, closely apposed membranes which are not fused and do not form tight junctions or external compound membranes. The continuous nature of the dense material of the terminal bar around the circumference of the cell suggests that this material could form a structural brace, holding the cells more closely apposed.

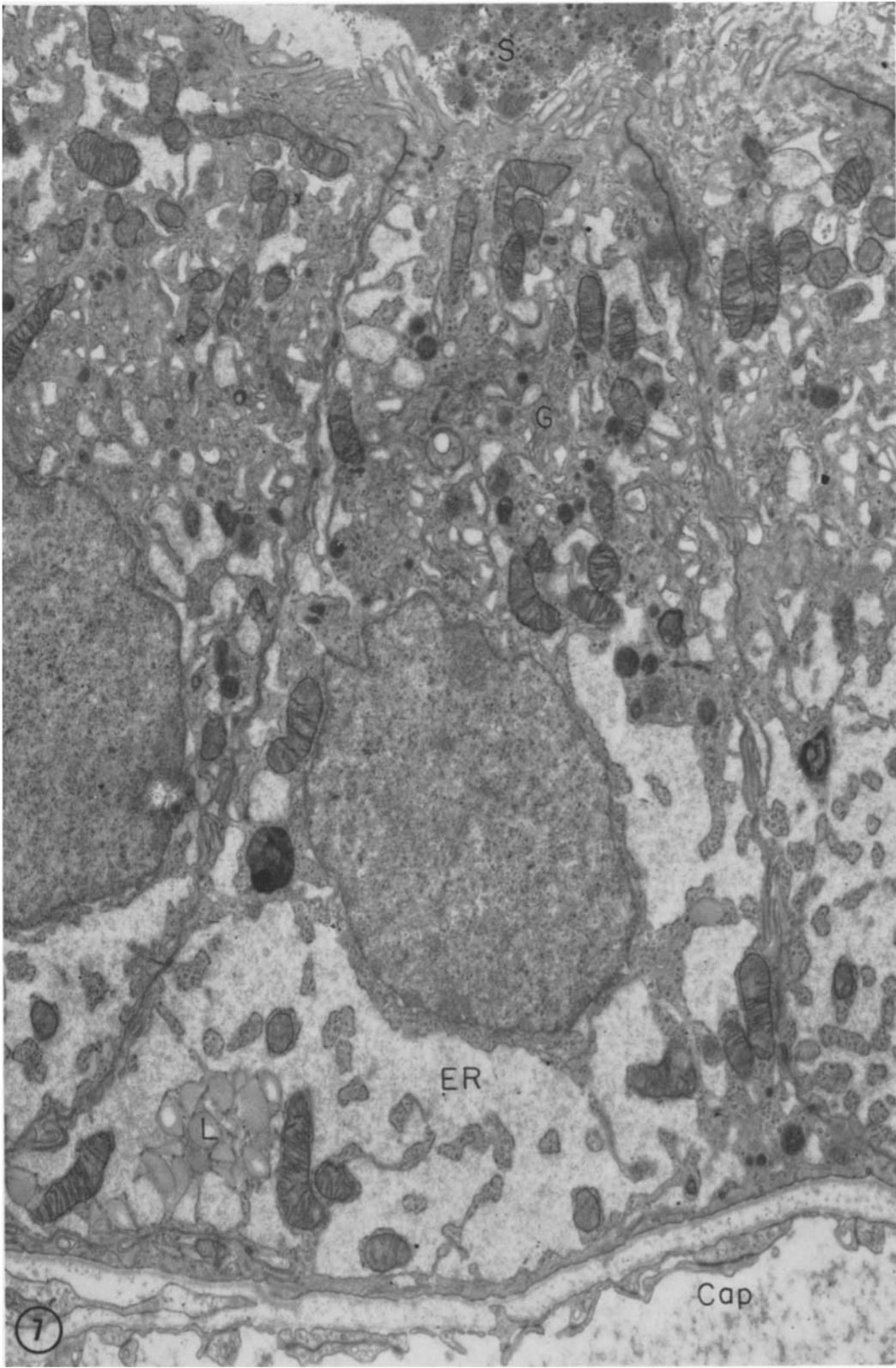
A peculiar feature of the gland cells from the delay period is the presence of unusually large

mitochondria. It is apparent that the spheroidal structure of these mitochondria, taken together with the structure of the cristae, would mean that the area of internal mitochondrial membrane is relatively large in comparison to that of the external mitochondrial membrane. However, it is also apparent that unusually large diffusion distances to the cristae would be present in these mitochondria, compared to the more normal elongated forms of mitochondria or to the unusually large but elongated mitochondria of some muscles, such as insect flight muscle (39).

It would be interesting to know whether the presence of these mitochondria is necessarily correlated with low levels of progesterone and what the physiological significance of their peculiar form may be. As previously noted, the association of large mitochondria with the glycogen-rich basal regions of the gland cells of the human endometrium during the luteal phase has been reported by several groups (21, 24, 36, 40). Nilsson (36) suggests that the function of these mitochondria is related to the glycogen-rich material produced in the basal portions of these cells. Since there is no correlation between the regions of histochemically demonstrable glycogen and the basal regions of the gland cells of delayed implantation in mink, such a function should not be attributed to the unusually large mitochondria in this species.

The alteration of the morphology of the gland cells from delayed implantation to late delay and early implantation stages is striking, and suggests a change in either the rate of secretion or the nature of secretion, or both. Many more secretion granules are present in the gland cells of delayed implantation than at later stages. However, the presence of granules in the cytoplasm is an indication of accumulation of secretion, but by itself is not a good indication of the rate of extrusion. A number of features of the gland cells from the late delay and postimplantation stages suggest a high rate of secretory activity. These

FIGURE 7 These gland cells in the endometrium of mink in an early post implantation stage demonstrate the changes which occur in the late delayed implantation and early implantation stages. The dilated endoplasmic reticulum (*ER*), basally situated lipid droplets (*L*), normal-sized mitochondria, and irregular Golgi membranes (*G*) are characteristic of this stage. Note also the numerous microvilli and secretion (*S*) in the lumen, and that terminal bars are still a conspicuous feature of these cells. *Cap*, capillary. $\times 13,000$.



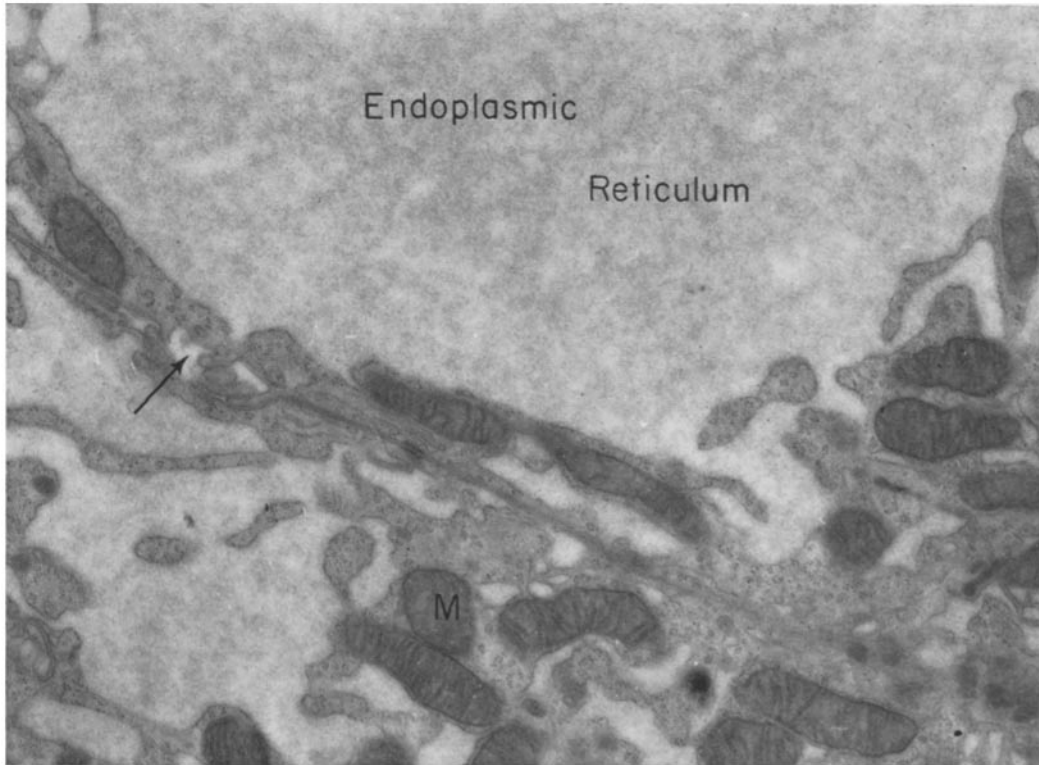
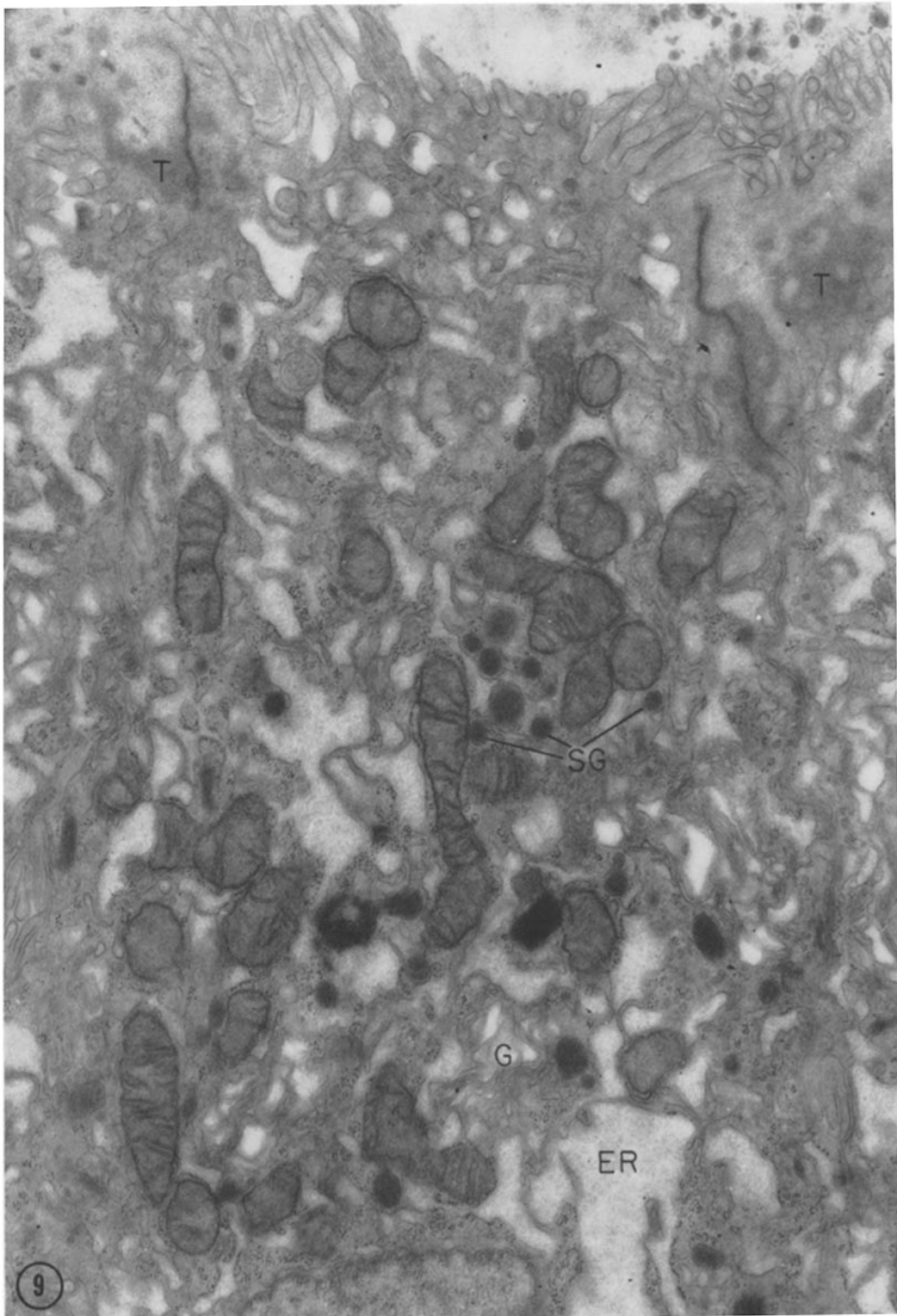


FIGURE 8 Many of the gland cells in the post implantation period show extreme dilation of the cisternae of the endoplasmic reticulum in the infranuclear region, as is illustrated here. Note the intercellular space along the margin of the cells (at the arrow). *M*, mitochondrion. $\times 24,000$.

features include the highly dilated endoplasmic reticulum, the presence of small granules in the Golgi zone, the more normal mitochondria, and the increase in elaboration of the free surface. Indeed, these cells resemble in the extent of dilated cisternae the secretory cells of the anterior lobe of the mouse and rat prostate (3, 4) and the oviduct of the hen (23, 44), which glands produce copious quantities of protein secretion. It seems probable, therefore, that the gland cell in the late delay and post implantation stages is a highly active secretory cell, whereas the gland cell in delay is accumulating secretory granules, but forming and releas-

ing them less rapidly. On the basis of this interpretation, a secretory pathway can be postulated in which the intermediate products of synthesis would accumulate in the endoplasmic reticulum, pass to the Golgi region where fluid is removed and secretion granules formed, and then progress through the apical region of the cell to release at the luminal cell membrane. It should be noted that the Golgi cisternae do not contain demonstrable granules, and that their contents are less electron opaque than those of the cisternae of the endoplasmic reticulum. Thus, while the Golgi cisternae might be involved in removing fluid

FIGURE 9 This section of the apical, Golgi, and supranuclear regions of gland cells in a post implantation stage is cut tangentially. The terminal bar material (*T*) is prominent, and some of the Golgi cisternae are dilated (*G*). Note the close association of the endoplasmic reticulum (*ER*) with these Golgi regions, and the presence of small granules (*SG*). $\times 25,000$.



from the secretion, they would not seem to actually contain the secretory material at any stage of the process.

Only the secretion granules of cells in the delay period reach sufficient size and abundance to be visualized with the light microscope. In previous studies, these granules were largely overlooked, while alkaline phosphatase and mucopolysaccharides were reported in the apical regions of these cells (10, 12, 15). These latter substances, however, undergo only minor changes (increases) at the end of the delayed implantation period and do not seem to correspond to the secretion granules. Nor have the polysaccharide fringes, known to be present in other species (27, 41), been visualized as secretion granules by electron microscopy. The size and density of the granules, and their relative insolubility in organic solvents as well as water, probably indicate that they are protein in nature. After fixation for electron microscopy, the granules can be visualized in sections of methacrylate- or epoxy-embedded material by toluidine blue staining or with periodic acid-Schiff methods. The PAS reaction cannot be considered specific for polysaccharides after fixation in osmium-containing fixatives since carbonyl groups may be formed in other substances by the prior oxidation with the fixative. However, since there is little reason to suspect the presence of lipid compounds in these granules, they probably do contain polysaccharide. That protein granules containing polysaccharide can be visualized in electron microscope preparations of this sort has been demonstrated in the pituitary gland (1, 18; see Purves (38) for a discussion of

whether it is the glycoprotein hormones that are visualized), the secretion of the seminal vesicles (7), and the thyroglobulin of the thyroid (43). It is likely, therefore, that the secretion granules are proteinaceous, and contain polysaccharide, but they are not associated with the PAS-positive fringe seen with the light microscope or with the alkaline phosphatase activity in this area.

It has long been known that the products of glandular secretion contribute to the embryotroph once implantation has occurred, and that a progesterational uterus is necessary for implantation, but there is little evidence available in any species to indicate whether the products of the uterine glands, the activity of the luminal epithelium, or altered diffusion from blood vessels are of particular importance in the formation of an intrauterine environment which is favorable to implantation *per se*. Recent work on the rabbit has tended to de-emphasize the importance of the glandular epithelium in the initiation of implantation in this species (2, 20). It is particularly interesting to find in the mink such major alteration in the morphology of the uterine glands prior to implantation. While the evidence for enhanced secretion does little to delineate the specific role of the glands, it should, nevertheless, focus our attention on the function of these structures in relation to implantation.

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