

## The “Clear Cells” of Human Endometrium

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*Summary.* The “clear cells” described by Feyrter in human endometrium were investigated with light and electron microscope in normal endometrium, hyperplasia and polyps. The “clear cells” of Feyrter correspond to cells in the ciliogenesis process and wandering cells: histiocytes and large lymphocytes. In human endometrium there are no cells with an ultrastructural pattern of the endocrine type.

In the glandular epithelium of human endometrium Feyrter (1938, 1949 and 1952) described the presence of “clear cells” with an active endocrine function. He included them among the cells of the diffuse endocrine epithelial organ or “clear cells system” and described them as cells lying more often on the base side of the epithelium than on the lumen side, having a chromophobe cytoplasm and frequently with the aspect of globular cells with a pale round nucleus. These morphological features make them different from the normal gland epithelial cells, which are darker and with an elongated and more dense nucleus. Feyrter has pointed out that these clear cells are especially abundant in glandular-cystic hyperplasia and in polyps.

After the descriptions of Feyrter other authors have also studied these cells under the light microscope. Müller (1951) agrees with Feyrter in considering them as endocrine cells. On the contrary, Rotter and Eigner (1949/50) conclude that the clear cells correspond to degenerate epithelial cells. Sarbach (1955) and Jakubovits (1955) reach a similar conclusion. Hamperl (1950) in a study on the ciliated cells of the human endometrium, considers that the cells described by Feyrter correspond to epithelial cells bearing cilia, denying the existence of any other type of clear cells apart from the ciliated and lymphocytes. Besides degenerate cells and those bearing cilia, Fuchs (1959) admits as clear cells the usual epithelial cells which are preparing for mitosis. One of us (Vázquez, 1964) holds the opinion that the clear cells described by Feyrter include, besides the ciliated cells, wandering cells, especially histiocytes.

At present no agreement exists about the nature of the clear cells. In the present work we present our findings with light and electron microscope on the different types of clear cells, especially on the cells of the characteristics described by Feyrter.

### Material and Methods

Fifty endometrial specimens were obtained by curettage or by hysterectomy. Five cases were in normal proliferative phase, 20 in normal secretory phase and 25 belonged to glandular

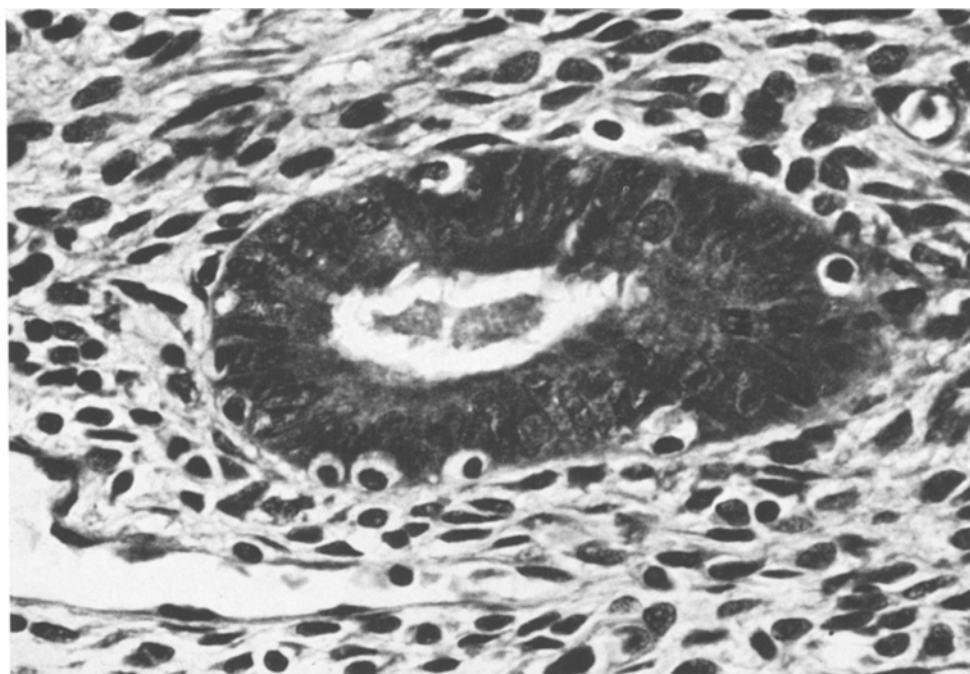


Fig. 1. Endometrial polyp. Wandering cells located in the epithelial lining against the basement membrane. HE  $\times 450$

hyperplasia with or without secretory changes. Small blocks of tissue were fixed for 1 to 5 hrs in 4% cacodylate buffered glutaraldehyde and postfixed in 1% phosphate buffered osmium-tetroxide 1 hr. The tissue was embedded in Epon 812. Ultrathin sections were double stained with uranyl acetate and lead hydroxide and examined with a Siemens Elmiskop 1A electron microscope.

In order to establish the correlation between electron and light microscope findings, semithin sections, ranging from 0.5 to 1  $\mu$  in thickness, were made before and after the ultrathin sections. They were picked up on coverslips and attached to the glass by mild heating. The Epon was removed with sodium (Mayor *et al.*, 1961). These sections were stained with methylene blue.

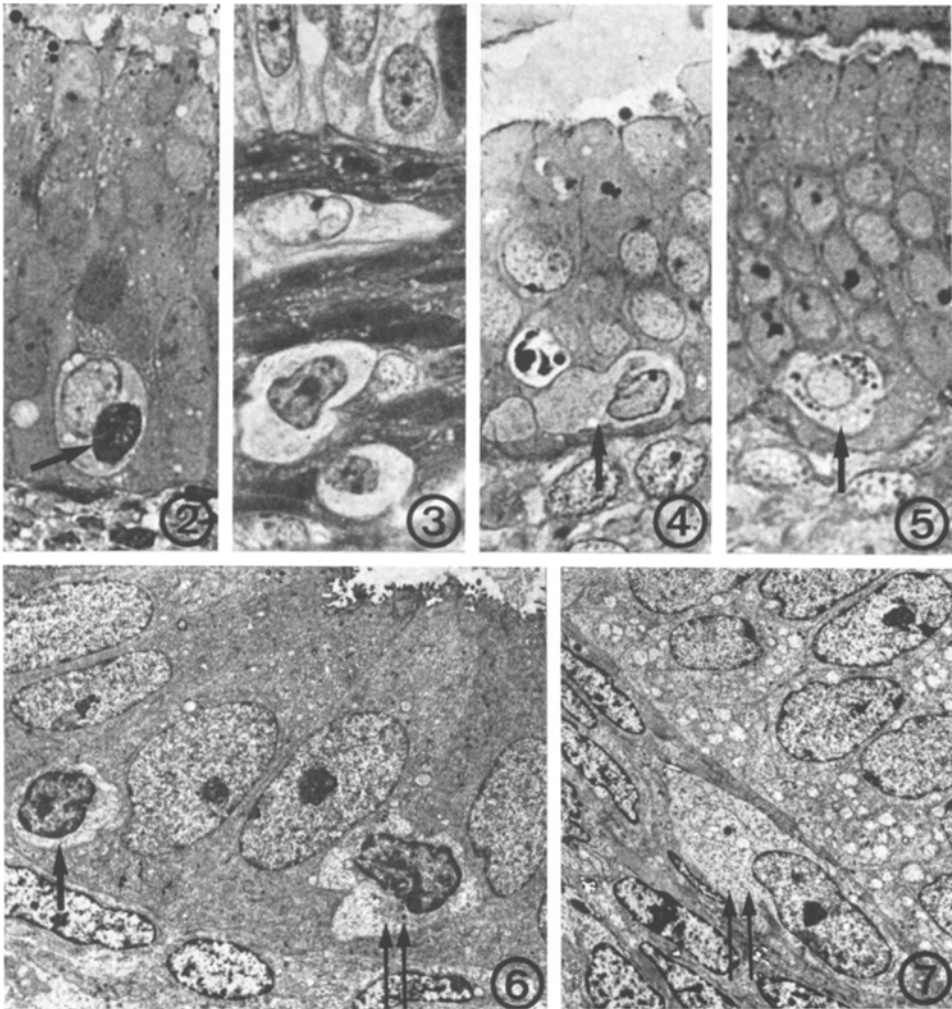
Paraffin sections was performed in formalin fixed material for conventional light microscopy.

## Results

### 1. Epithelial Cells

With light microscope in semithin sections and with electron microscope two types of epithelial cells have been observed in the layer which lines the glands and in the superficial layer which covers the uterine cavity: a) the normal epithelial cells and b) ciliated cells.

a) The normal epithelial cells have a cytoplasm which is more or less dense according to the degree of hydration. This has permitted to distinguish between "more dense" and "less dense" cells. Both present the same proportion of organelles, identical ultrastructural pattern, and have between them desmosomes



Figs. 2—5. Semithin sections of the material embedded in Epon ( $\times 1100$ ): 2) Epithelial cell located in the basal portion of the glandular epithelium with a subnuclear vacuole containing cilia (arrow); 3) Wandering cells in stroma; 4 and 5) histiocyte (arrow) in epithelium

Figs. 6—7. Electron micrograph illustrating part of a gland and stroma: 6) Two wandering cells, a lymphocyte (arrow) and a histiocyte (double arrow), located in the epithelium ( $\times 1600$ ); 7) Wandering cell in stroma (double arrow) ( $\times 1800$ )

and interdigitating processes; the latter are especially abundant during the secretory phase. In the apex they have secretory granules up to one micron in diameter, more abundant in the late proliferative phase and especially in hyperplasia.

b) Ciliated cells are found scattered in the epithelium or forming groups of two and more rarely of three elements. They are very abundant in hyperplasia, frequent in the proliferative phase and scarce in the secretory phase.



Fig. 8. Histiocyte (*H*) containing dense granules located in the base side of the glandular epithelium against the basement membrane (arrows)  $\times 5400$

The cytoplasm is very clear, contrasting with the density of the cytoplasm of the neighbouring cells (Fig. 2). Nevertheless, ciliated cells also exist with a cytoplasm as dense as that of the normal epithelial cells. The process of ciliogenesis in these cells has been studied by Hamperl (1950) using the conventional histological methods. We have studied this process with light microscope in semithin sections and with electron microscope; the detailed results will be given in another report. The process of ciliogenesis starts with subnuclear vacuoles containing cilia in cells located in the basal portion of the epithelium near the basement membrane (Fig. 2). These cells elongate towards the glandular lumen. At the same time the vacuole migrates to the top of the cell. When the cell reaches the lumen, the vacuole fuses with the plasma membrane and the cilia project in the lumen. The ciliated cells show ultrastructural features similar to the those of the neighbouring epithelial cells apart from the cilia and the presence of a clearer cytoplasm. On the other hand, like the cells usually found, they reveal the presence of secretory granules in the apex, desmosomes and they also actively synthesize glycogen when the glands undergo secretory change.

## 2. *Wandering Cells*

In the epithelial lining there are also wandering cells, scattered or in groups of two. They have a very clear cytoplasm, which does not accept the staining and

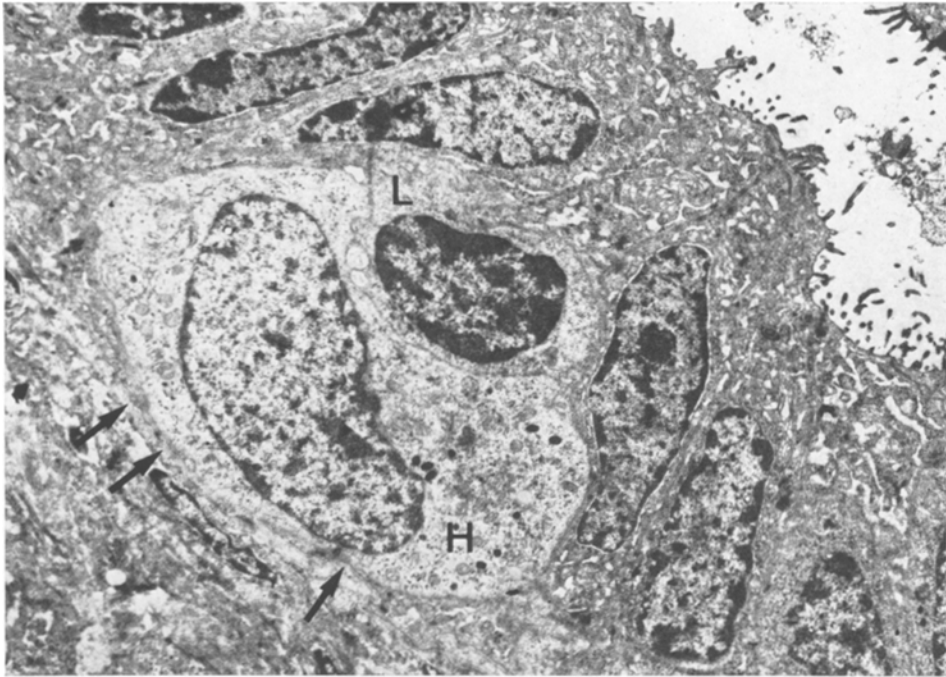


Fig. 9. Histiocyte (*H*) and lymphocyte (*L*) in close contact located in the basal portion of the epithelium; arrows basement membrane,  $\times 8600$

offers a very low electron density. They have a round shape and smooth surface, but they may present a broad cytoplasmic expansion (pseudopod). They are predominantly located against the basement membrane displacing sideways the neighbouring epithelial cells. Wandering cells, more numerous in hyperplasia (Fig. 6), are particularly abundant in endometrial polyps (Fig. 1).

Two main types of wandering cells can be distinguished according to cell size, nuclear structure and cytoplasm content: lymphocytes and histiocytes. The lymphocytes which are much more abundant, show the typical ultrastructure of those present in other tissues, but they have a larger cytoplasm of less electron density. There are small and large lymphocytes. The histiocytes are of a larger size (Fig. 4), with a Kidney-shaped nucleus and clear cytoplasm containing lysosomes and phagocytosed fragments of chromatin (Figs. 5 and 8). Both types of cells are frequently associated, establishing a close contact which may end in the complete phagocytosis of the lymphocyte by the histiocyte (Figs. 9 and 10).

The wandering cells come from the stroma, where they can be observed in semithin sections (Fig. 3) and with electron microscope (Fig. 7). From the stroma they migrate through the basement membrane (Fig. 11) and penetrate in the epithelium. Some of these cells may even reach the lumen, where they acquire a foamy cytoplasm, with phagocytosed cell debris and at times they are binucleated.

Polymorphonuclear leucocytes may be also present in the epithelium, especially in cases of endometritis.

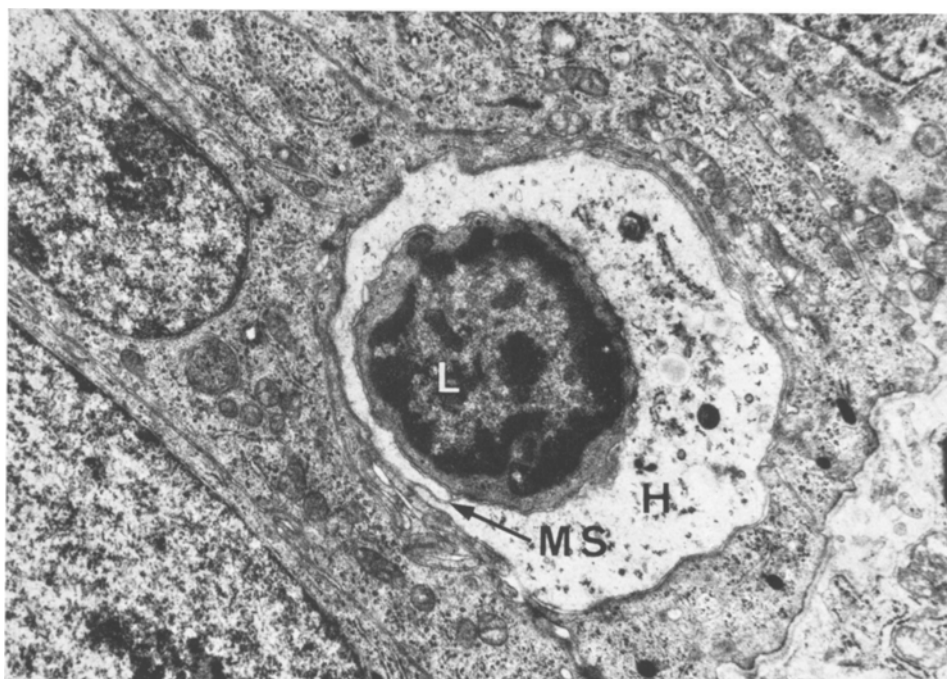


Fig. 10. A histiocyte (*H*) completely surrounds a lymphocyte (*L*), *MS* Overlapping of the cytoplasmic expansion, with two plasma membranes showing a meso-like structure,  $\times 19800$

### Discussion

In human endometrium there are two types of cells which have the characteristics described by Feyrter as “clear cells” belonging to the “diffuse endocrine epithelial organ”: cells in ciliogenesis process and wandering cells (histiocytes and large lymphocytes).

The identification of the ciliated cells with the clear cells of Feyrter was made by Hamperl (1950) under light microscope, a fact that we verify with electron microscope. At the beginning of the process these cells are localized at the base of the epithelium and often have a clear cytoplasm. They may be made more evident under light microscope, staining frozen sections with tartric thionin of Feyrter, or in semithin sections.

In answer to Hamperl, Feyrter (1952) points out that the clear cells described by him may or not be ciliated. Moreover, not all cells bearing cilia have a clear cytoplasm. In fact we have been able to verify that many ciliated cells have a cytoplasm as dense as that of the usual epithelial cells. However, we deal with only one cell type, the different density of the cytoplasm being caused by the degree of hydration.

Feyrter emphasizes that the presence of cilia in these cells does not mean they do not belong to the endocrine system. However, the ultrastructural features are



Fig. 11. Wandering cell migrating through the basement membrane (arrows),  $\times 14000$

similar to those of the usual epithelial cells. Furthermore, they do not have the ultrastructural pattern of endocrine cells, that is to say either secretion granules stored in the basal portion of the cell, in relation to their release into capillaries in cells that secrete proteins, or very numerous mitochondria with prevailing tubular cristae and prominent smooth endoplasmic reticulum in cells that secrete steroid hormones. The ciliated cells may have dense granules, but these are localized in the apex like in the normal neighbouring cells, and the smooth endoplasmic reticulum is very rarely observed.

Most of the Feyrter's "clear cells" correspond to wandering cells, histiocytes and large lymphocytes, particularly in polyps.

Similar cells are found in stroma and we have seen cells passing through the basement membrane (Fig. 11). The frequent fragments of chromatin in the vacuoles of the histiocytes are proof of their ability to phagocytose.

The frequent association between histiocytes and lymphocytes deserves a supplementary commentary. Leucocytes suffer a swelling because of hydration, when they pass through an epithelial layer. The swelling is followed by cellular death and lymphocytes with cariorrhesis are often observed in the epithelium. Therefore histiocytes emerge from stroma and gather in the epithelium and phagocytose the cellular debris, becoming macrophages.

Some histiocytes reach the glandular lumen. Here they mingle with mucopolysaccharides and show a foam cytoplasm. This is more often seen in the cystic

glands of hyperplasia. Degenerated epithelial cells (Rotter and Eigner, 1949/50; Ratzenhofer and Schmid, 1954; Sarbach, 1955; Fuchs, 1959) and those at the beginning of the mitosis (Fuchs, 1959) may also show a clear cytoplasm, as Feyrter's cells. The often show cariorresis and resemble macrophages under light microscope. Under electron microscope these degenerated cells are scarcely observed.

We do not want to enter into discussion about the local or hematogenous origin of the histiocytes. What we have said concerning the clear cells of the endometrium, is not to be applied to the clear cells of other organs.

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