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The Rat Pituitary Cleft: A Correlated Study by Scanning and Transmission Electron Microscopy

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Summary. SEM reveals that the inner surface of the pituitary cleft is lined by a continuous layer of marginal cells possessing microvillous and ciliated apical surfaces. The ciliated cells are more numerous on the posterior side (toward the pars intermedia) than on the anterior side of the cleft (toward the pars distalis). In contrast small infoldings (crypts) were occasionally noted only on the marginal layer covering the distal part of the hypophysis. In some areas of the cleft the surface features of the marginal cells are rather similar to the epithelial cells populating the upper parts of the respiratory tract in their topography and distribution. In other regions they also show striking similarities with the ependymal cells (tanycytes) lining the lateral recesses of the 3rd ventricle and the infundibular process with which the pituitary cleft has a very close topographical relationship.

The parenchymal cells of the pars distalis are closely related to the flattened marginal cells of the cleft. The intercellular spaces of the pars distalis form a three-dimensional labyrinthic series of cavities continuous with the submarginal spaces of the cleft. Further SEM and TEM results demonstrate that the majority of the microvillous marginal cells lining both sides of the cleft possess surface features such as bulbous protrusions, laminar evaginations and large cytoplasmatic vacuoles, which are very likely the expression of an active transport of fluids.

On the basis of these results it is concluded that the fluid-like material (colloid) present in the pituitary cleft is mainly derived from the fluids contained in the lacunar spaces of the pars distalis. Thus, marginal cells by absorbing fluids from the cleft by active endocytosis, may transport to the pars intermedia material (or hormones) produced in the distal part of the gland and vice versa.

The cilia present on many marginal cells, based on their 9+2 tubular pattern, possess a kynetic role. This is very similar to that shown by the ciliated cells of the ependyma lining the brain ventricles. The occurrence of ciliated cells

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within the pituitary parenchyma (mainly in the follicles) suggests that they probably arise from the ciliated cells populating the marginal layer of the cleft and with which the parenchyma cells are closely related.

Key words: Pituitary – Rathke's cleft – Ultrastructure – Scanning electron microscopy – Rat

It is commonly believed that the pituitary cleft, occurring in various vertebrates, represents the original recess of the so-called Rathke's pouch derived in the embryo from the ectodermal evagination of the stomodeum (Hamilton et al. 1973; Langman 1975). In the rat and other mammals this recess persists during postnatal life as a wide fissure separating the pars distalis from the pars intermedia. It is lined by a continuous layer of cells ("marginal cells") and contains a fluid-like material (colloid) of uncertain function, origin and chemical composition (Kurosumi and Fujita 1975).

The pituitary cleft has been reported in a few ultrastructural studies and its submicroscopic arrangement has been discussed with special reference to: (1) the role of the marginal cells in colloid formation (Dubois and Girod 1970; Vanha-Perttula and Arstila 1970; Dingemans and Feltkamp 1972; Ciocca and Gonzales 1978; Ciocca 1980), and (2) cleft cells as a possible "renewal cell system" (Yoshimura et al. 1977) due to the similarity between marginal cells and follicular cells of the hypophysis (Kagayama et al. 1969; Sano and Sasaki 1969; Vila-Porcile 1972).

This paper presents original information on the fine structure of the rat pituitary cleft by scanning electron microscopy (SEM) for the purpose of analysing the topographical arrangement and surface features of the marginal cells. Transmission electron microscopic (TEM) results are also reported with the aim to better evaluate the nature of the marginal layer of the cleft and its relationship to the subjacent endocrine cells of the pars intermedia and pars distalis. Some of our SEM results have been presented in a earlier preliminary report (Correr et al. 1979).

Materials and Methods

Hypophyses of 20 adult albino rats were used. The animals were anesthetized with an intramuscular or intraperitoneal injection of Nembutal (0.1 ml/Hg/animal) and perfused through the left ventricle with heparinized Tyrode solution at room temperature. Gravity maintained a perfusion flow of about 60 ml/min. After 30 s the flow of the solution was interrupted and 2.5% glutaraldehyde buffered with cacodylate (0.10 M; pH 7.4) was perfused for about 5–10 min. After perfusion, the skull of each rat was opened and the hypophysis, carefully removed and immersed in the same buffer, was prepared in order to show the cleft.

For SEM. After immersion in the same fixative for 12–72 h pituitary glands were washed in the buffer and distilled water several times, dehydrated in increasing concentrations of acetone and critical-point dried liquid CO_2 using Sorvall apparatus. The specimens were mounted on metal stubs using conducting silver paint and were coated with gold in a sputter coater (Edwards 150).

A Cambridge 150 scanning electron microscope operating at 10–15 kV was used for observations and photographs.

For TEM. Tissues were postfixed in OsO_4 and then washed in cacodylate buffer and distilled water several times. After dehydratation in ethanol, the samples were embedded in Epon 812. Thin sections stained with uranyl acetate and lead citrate (Venable and Coggeshall 1965) were viewed in a Zeiss EM 9A electron microscope.

Results

The anterior lobe of the pituitary gland in the adult rat is clearly separated from the intermediate lobe by a wide fissure lined on both sides by a continuous layer of cuboidal cells ("marginal cells").

An amorphous material, having a different electron density and likely corresponding to the colloid, may appear well preserved in some specimens in various areas of the opened cleft being still adherent to the surface of the marginal cells (Figs. 1, 2). The colloid is rather dense and abundant mainly in the lateral recesses of the cleft where the marginal cells lining the pars anterior come into close contact with those covering the pars intermedia. In the central part of the fissure the colloid has a watery consistency and a very low electron density (Figs. 1, 2). In a few cases the continuous luminal surface of the cleft is apparently interrupted by some small regions of attachment between the pars intermedia and pars distalis which seem to divide the pituitary fissure into some smaller cavities (Fig. 3).

The anterior marginal layer of the cleft when observed by SEM shows a cellular surface provided with a varying number of microvilli ("microvillous cells") and other apical surfaces possessing long cilia. On this side of the cleft, the microvillous cells are more abundant than the ciliated cells which generally occur isolated or associated in small groups. Other cellular types possessing a single short cilium or a reduced number of cilia together with cells showing predominantely smooth surfaces with rare microvilli are also present (Figs. 4, 5). Other cells have a large size and a rounded shape and in addition to the microvilli show bulbous protrusions and laminar extensions (Figs. 6, 7).

Under the SEM, the continuity of the marginal layer covering the distal part of the gland appears interrupted in some areas by small irregular openings through which the smooth apical surfaces of subjacent cells are evident (Fig. 8). In other instances, the marginal cells are infolded into the underlying glandular parenchyma of the pars distalis forming discrete crypt-like invaginations (Fig. 9). Cells provided with irregularly distributed cilia and/or microvilli are also noted apparently free on the surface of the anterior and posterior sides of the pituitary cavity (Fig. 10).

When observed by TEM, the marginal cells lining the anterior part of the cleft are closely associated with the parenchymal cells of the pars distalis. The marginal cells form a single layer of irregularly flattened elements which can be reduced to very thin cytoplasmic extensions or in other cases may appear as a simple cuboidal epithelium provided with long cilia (Figs. 2, 11).

As revealed by parallel SEM and TEM observations, the majority of the cells covering the distal part of the pituitary cleft are very flattened and their cell bodies are provided with numerous thin and irregular extensions (Figs. 2, 11). These, which may assume the features of filopodia when observed in SEM preparations (Fig. 12), come into close contact with similar evaginations of adjacent cells and subjacent stellate cells (Vila-Porcile 1972), where they form typical junctional complexes (Figs. 2, 13). In this way the marginal cells and the stellate cells form a series of irregularly shaped spaces in which are contained the rounded and smooth surfaced parenchymal cells (endocrine cells). These in turn are immersed in a watery fluid-like material having the same electron density as that present in the adjacent lumen of the pituitary cleft (Fig. 11). In a few cases the barrier limiting the lumen of

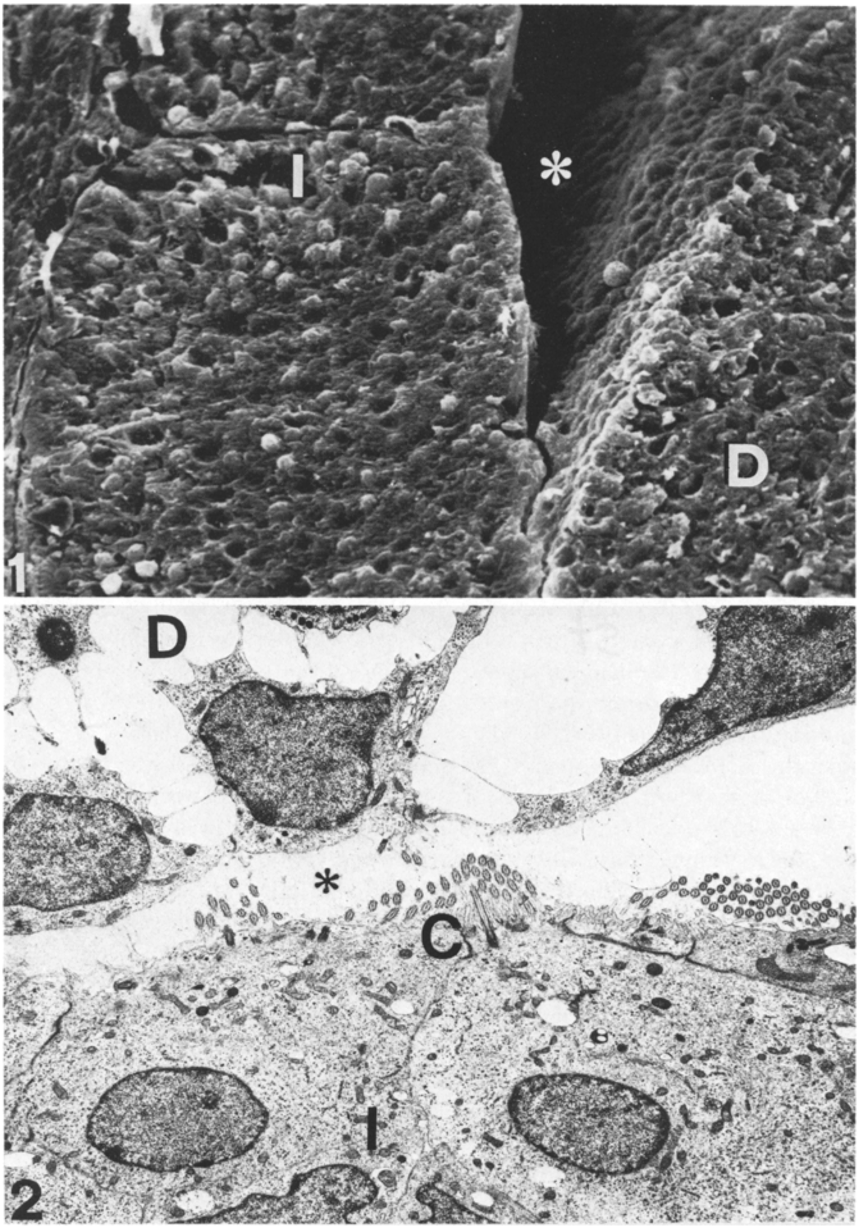


Fig. 1. The Rathke's cleft (*asterisk*) between pars distalis (*D*) and intermedia (*I*). SEM; × 1,200

Fig. 2. Marginal cells of the Rathke's cleft covering the pars intermedia (*I*) and distalis (*D*). Some marginal cells possess numerous cilia (*C*) and others are very flattened (opposite side). A fluid-like material is contained into the lumen of the cleft (*asterisk*). TEM; × 4,320

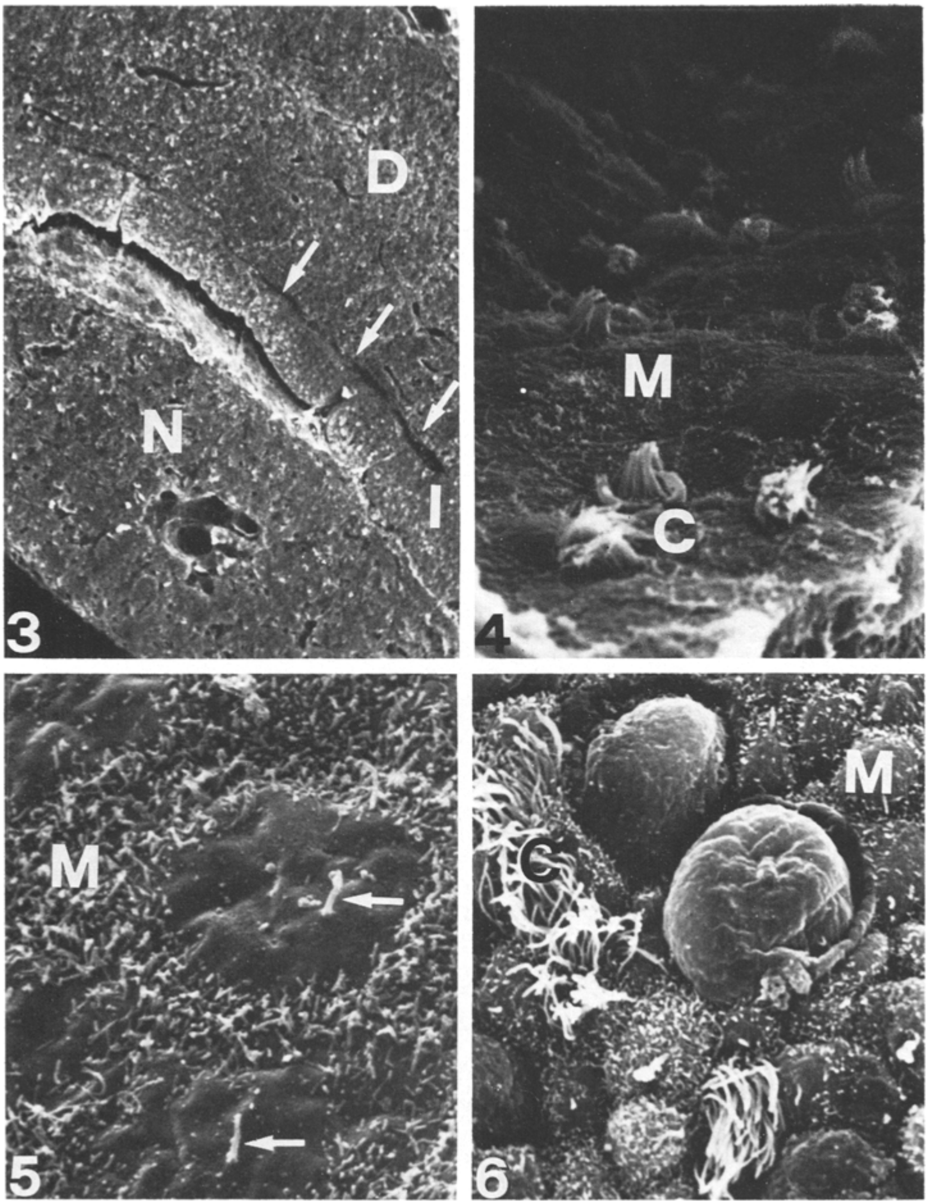
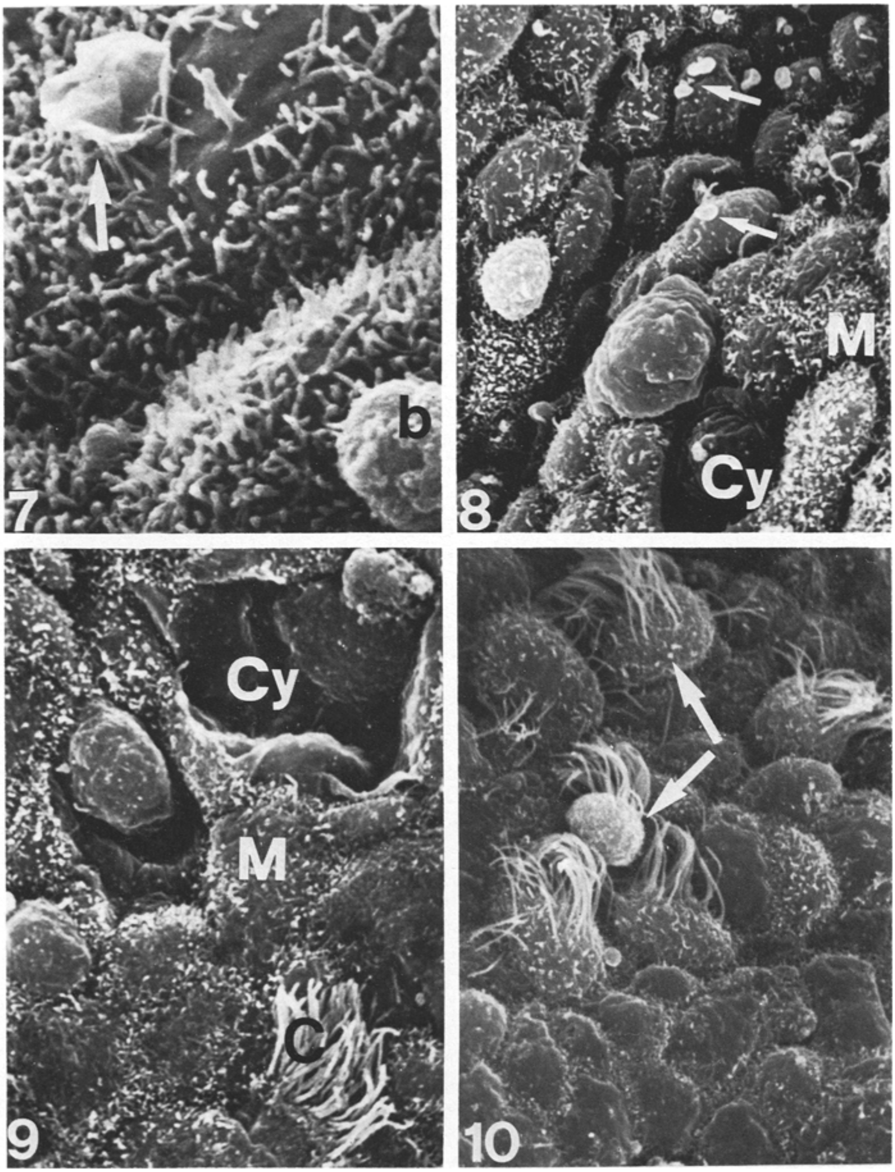


Fig. 3. Small regions of attachment (*arrows*) between the pars intermedia (*I*) and distalis (*D*) divide the pituitary cleft in small cavities. *N* neurohypophysis. SEM; × 180

Fig. 4. Ciliated (*C*) and microvillous cells (*M*) covering the anterior part of the Rathke's cleft toward the pars distalis. SEM; × 3,150

Fig. 5. Cells with apical surfaces provided with microvilli (*M*) and isolated cilia (*arrows*) on the anterior side of the cleft. × 13,500

Fig. 6. Ciliated (*C*) and microvillous cells (*M*) closely related to large and smooth rounded marginal cells on the anterior part of the cleft. × 3,600



Figs. 7–10. Features of marginal cells lining the anterior side of the pituitary cleft (toward the pars distalis) as viewed by SEM

Fig. 7. The apical surface of some cells provided with microvilli is rather smooth and shows bulbous protrusions (*b*) and laminar extensions (*arrow*). ×18,000

Figs. 8 and 9. Marginal layer of the cleft infolded into the subjacent parenchyma thus forming crypt-like invaginations (*Cy*). *M* microvillous cells, *C* ciliated cells; some elements have smooth apical surfaces and possess numerous small blebs (*arrows*). ×3,600

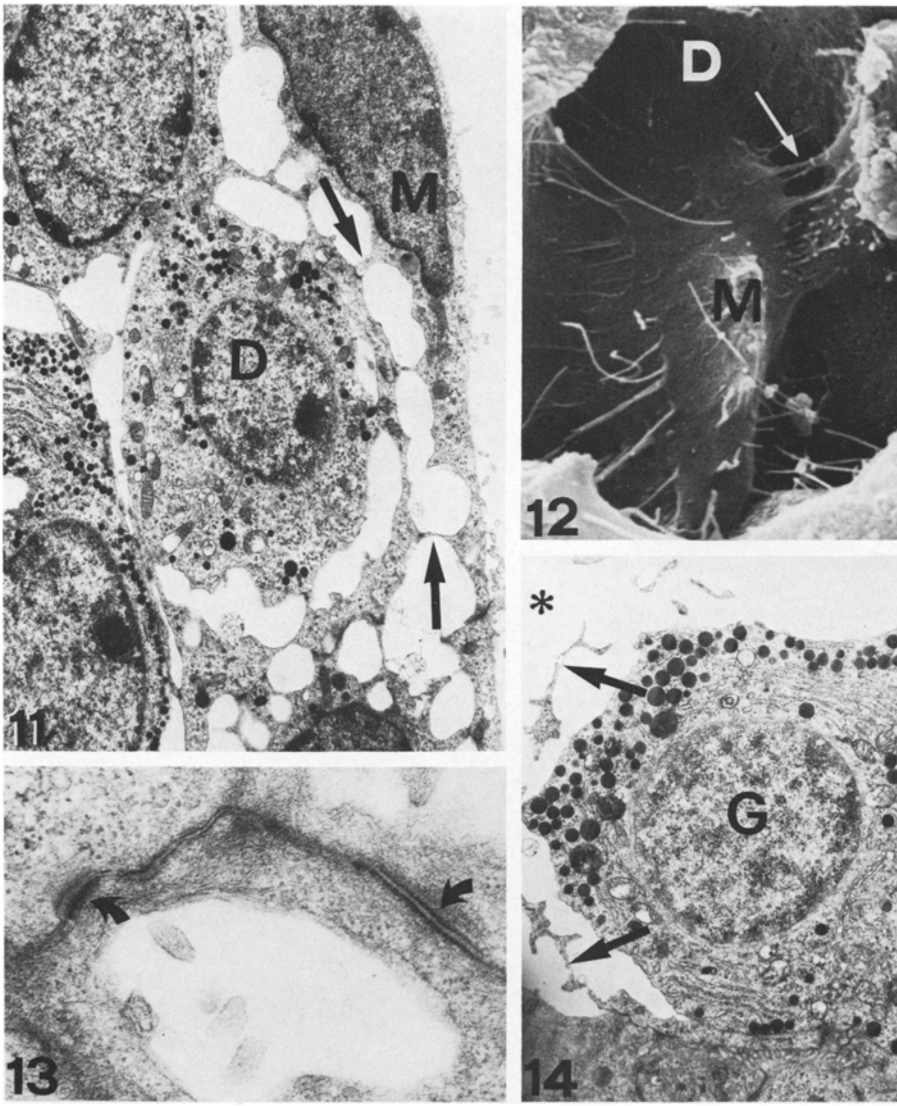


Fig. 10. Ciliated cells in apparent desquamation free on the luminal surface of the pituitary cleft (*arrows*). SEM; ×3,600

Figs. 11–13. Marginal layer (*M*) covering the parenchymal tissue composing the pars distalis (*D*). The marginal cells (*M*) are flattened and possess numerous and thin irregular extensions (*arrows*). These coming in close contact with other evaginations of adjacent cells form typical junctional complexes (*arrows* in **Fig. 13**). The endocrine cells of the pars distalis (*D*) are also covered by such cellular extensions (**Fig. 11**, TEM; ×5,270; **Fig. 12**, SEM, ×8,500; **Fig. 13**, TEM, ×30,600)

Fig. 14. Glandular cell of the pars distalis (*G*) bulging into the pituitary cleft (*asterisk*) covered by very thin extensions of marginal cells (*arrows*). TEM; ×7,140

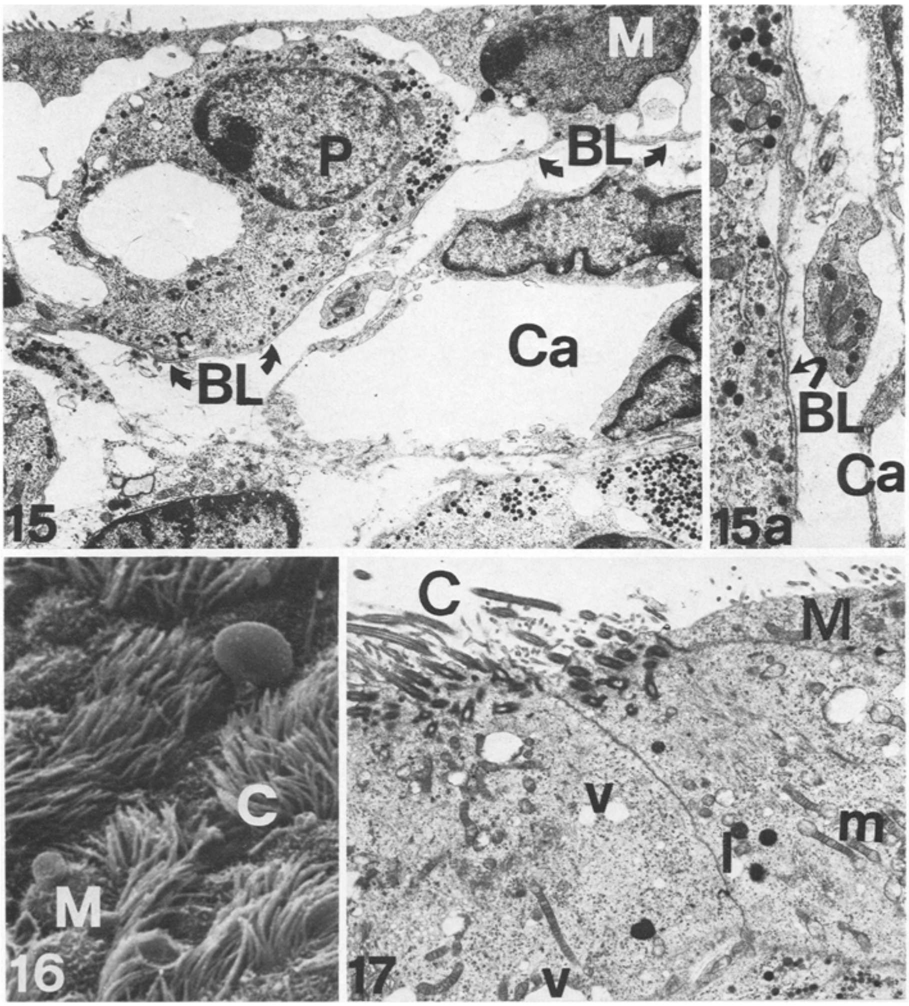


Fig. 15. A thin basal lamina (*BL* plus *arrows*) covers the surface of parenchymal (*P*) and marginal cells (*M*) in an area closely associated to a capillary wall (*Ca*). This area is magnified in the *inset* of **Fig. 15a** TEM. ×4,760; ×11,900

Figs. 16 and 17. Ciliated (*C*) and microvillous cells (*M*) covering the posterior side of the Rathke's cleft. Some of these cells are provided with large vacuoles (*v*), elongated mitochondria (*m*) and dense bodies (lysosomes) (*l*) (**Fig. 16**, SEM; ×3,400; **Fig. 17**, TEM, ×4,760)

the cleft is reduced to very thin extensions of two or more marginal cells and the parenchymal cells appear bulging into the pituitary fissure or may be free on its surface (Fig. 14). Junctional complexes are present only between marginal cells and not between marginal and parenchymal elements (Fig. 11). A delicate basal lamina, not always easily detectable, covers the surface of the parenchymal and marginal cells in the areas where they are closely related to the wall of blood capillaries (Fig. 15). Marginal cells of the anterior side of the cleft show large irregular nuclei with dense chromatin and scant cytoplasm containing few membranes of rough endoplasmic reticulum, polysomes, small mitochondria and a reduced zone of Golgi. Lysosomes, multivescicular bodies and large vacuoles are also occasionally present in these cells together with discrete bundles of microfilaments (Figs. 11, 15).

The marginal layer lining the posterior side of the cleft (i.e., related to the pars intermedia) has surface features generally similar to those already described for the anterior layer. Both ciliated and microvillous cells are evident but the elements provided with cilia are much more numerous here than on the anterior side. Their cilia are long and arranged in regular bundles (Figs. 2, 16). Cells with bulbous protrusions among microvilli are noted. Other elements having microvilli concentrated on the border of the cell and a centrally located single cilium are also frequently observed. Interruption or crypt-like invaginations of the marginal layer are not present on the posterior side. As a rule, the marginal cells of these zones have a characteristic epithelial arrangement as compared to those covering the anterior side of the cleft (Figs. 2, 16). If the SEM preparations are obtained by fracturing the cleft along an axis parallel to the marginal layer and control specimens are also observed under the TEM, the posterior marginal layer appears formed by polyhedral and/or columnar cells having the same features as a simple columnar epithelium. These cells are, as a rule, one layer thick but in some cases they may be arranged in two or more layers (a sort of stratified epithelium) occurring mainly in the areas corresponding to the lateral extensions of the cleft (Figs. 1, 2). A thick basal lamina always separates this epithelial layer from the glandular parenchyma of the pars intermedia (Fig. 17).

The cilia of these cylindrical cells possess a 9+2 tubular arrangement (Fig. 18). Both ciliated and microvillous cells have abundant cytoplasm with numerous elongated mitochondria, free polysomes and in many areas conspicuous bundles of microfilaments (Figs. 2, 17). Dense bodies and lysosomes appear concentrated mainly in the periapical areas of the cytoplasm where a discrete Golgi complex is also evident (Fig. 17). Large vacuoles and irregular apical protrusions are also noted on numerous cellular surface areas that are provided with microvilli. Both ciliated and microvillous elements are connected on their luminal borders by typical junctional complexes and the intercellular spaces are quite narrow (Figs. 2, 17).

In some TEM preparations, the marginal layer covering the posterior side of the cleft-which is always regularly lined by a thick basal lamina – is infolded in irregular and long recesses by the presence of elongated nerve fibers. These fibers, apparently arising from the connective tissue surrounding the vessels, penetrate the marginal cells and give rise in some zones to characteristic close contacts likely corresponding to cyto-neural (synaptical) neuroepithelial complexes (Fig. 18) similar to those revealed in the infundibulum in the pars intermedia proper (Kurosumi and Fujita 1975). Moreover the SEM analysis of the pituitary cleft shows that the marginal layer covering the anterior side of the fissure is in some zones evaginated in long finger-like projections measuring 40–80 μm in lenght. The evaginations are covered with flattened cells continuous with the marginal cells lining the cleft (Figs. 20, 21). The cell surfaces covering the villous-like projections possess numerous short microvilli and flattened microplicae (Fig. 21). Finally on both sides of the pituitary cleft occasional erythrocytes, parenchymal cells and other irregularly shaped elements of unknown nature (macrophages?) are present (Figs. 16, 20).

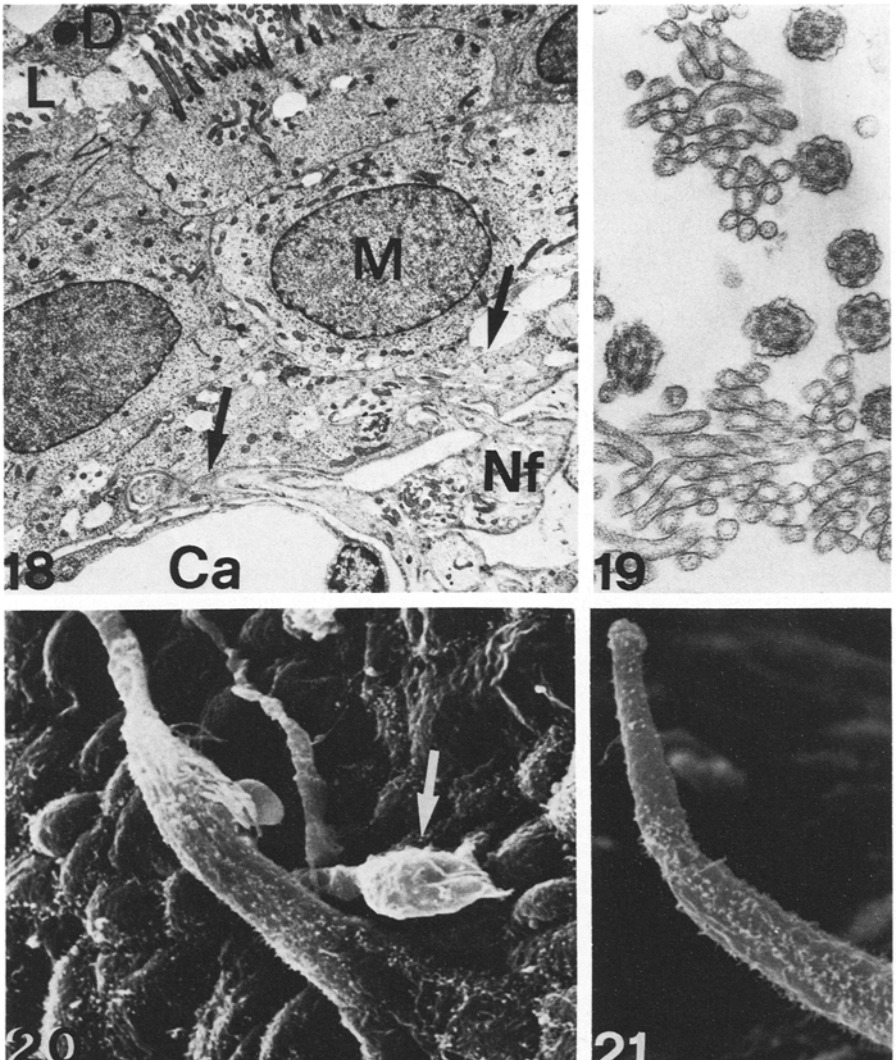


Fig. 18. Ciliated and microvillous cells composing the marginal layer (*M*) of the pituitary cleft related to the pars intermedia. Nerve fibers (*Nf*) arising from the subjacent areas are apparently infolding the basal lamina to come in close contact with the marginal cells (*arrows*). On the opposite side of the cleft the marginal cells lining the pars distalis are evident (*D*). *L* lumen of the cleft, *Ca* capillary. TEM; × 4,760

Fig. 19. Cilia (with 9+2 microtubular pattern) and microvilli belonging to marginal cells toward the pars intermedia. TEM; × 30,600

Figs. 20 and 21. Villous-like projections arising from the anterior side of the pituitary cleft. These are covered with flattened cells which are continuous with the marginal cells and possess numerous short microvilli (**Fig. 21**). Irregularly shaped cells, of unknown nature (macrophages?) are present over the marginal layer of the cleft (*arrow*); SEM (**Fig. 20** × 3,400; **Fig. 21**, × 3,400)

Discussion

The hypophysis of vertebrates is derived during the embryonal life from the interaction of cells arising from the ectoderm of the stomodeum (Rathke's pouch) and the neural ectoderm of the floor of the forebrain (infundibular process) (Hamilton et al. 1973). In the rat and in other mammals, the pars distalis of the adenohypophysis is clearly separated from the pars intermedia by a cleft which is commonly assumed to develop from the dorsal outpocketing of the roof of the primitive mouth (Sano and Sasaki 1969; Yoshimura et al. 1977).

SEM observations reveal that the inner surface of the pituitary cleft is lined by a continuous layer of epithelial-like cells (marginal cells) possessing microvillous and ciliated apical surfaces. The ciliated cells are more numerous on the posterior side (toward the pars intermedia) than on the anterior side of the cleft (toward the pars distalis). Small infoldings and/or other interruptions are occasionally noted, mainly on the marginal layer covering the distal part of the gland. The surface features of the marginal cells lining the pituitary cleft are rather similar in their topography and composition to the epithelial cells populating the upper parts of the respiratory tract (Andrews 1974; Smolich et al. 1977). The morphological similarity suggests that a relationship perhaps exists between these epithelial layers (Correr et al. 1979).

Studies on the development of the hypophysis by serial sections in chick embryos (Takor Takor and Pearse 1975) have suggested that the adenohypophysis is to be regarded as of neuroectodermal rather than ectodermal (stomodeal) origin, and thus the hypothalamo-hypophysial complex can be considered as a single rather than a composite entity. Reasons for accepting this alternate hypothesis reside also in recent concepts regarding the embryology of the diffuse neuroendocrine system and its relationship to the APUD cells, paraneurons or cells producing "common peptides" (Pearse 1969; Fujita 1977; Pearse and Takor Takor 1979). This hypothesis might also find support in recent immunocytochemical observations in which the brain-specific S-100 protein has been localized at the electron microscopic level in the anterior and posterior pituitary gland of the rat (Cocchia and Miani 1981).

Keeping in mind this possibility for the origin of the hypophysis, the marginal cells lining the cleft might be simply regarded as ependymal cells. If the surface features of the marginal cells of the cleft are compared to those of the ependymal cells lining the brain ventricles, it appears evident that they show numerous similarities (Kessel and Kardon 1979). In fact they both possess ciliated and non-ciliated cells having general distribution and surface morphology very easily comparable. The similarity is even striking if the marginal cells, as revealed in this study, are for example compared to the tanycytes lining the lateral recesses of the third ventricle and the infundibular process which are zones topographically very close to the pituitary cleft (Allen et al. 1978; Flament-Durand et al. 1978; Mestres 1978).

Regarding these morphological results as a further proof of the neuroectodermal origin of the hypophysis (Takor Takor and Pearse 1979), it may be logical to suggest that actually the pituitary cleft is nothing more than a closed cavity which was originally related to the hypothalamo-hypophysial recess (infundibulum) with which it shares similar origin, nature and possibly function. Thus also the marginal cells lining the pituitary cleft should be considered tanycytes and the occasional free cells on their surfaces may correspond to both macrophages (Kolmer cells) (Hosoya and Fujita 1973; Bleier 1975) and/or neuronal cells (supraependymal cells) (Mestres and Breipohl 1976; Coates 1977) observed in the brain ventricles (Allen 1975).

With regard to the relationship between pituitary cleft and glandular cells of the adenohypophysis, both SEM and TEM observations show that anterior marginal cells are closely related to the stellate and parenchymal cells of the pars distalis. With their long branches, often assuming the aspect of filopodia, they form a sort of three-dimensional labyrinth of narrow spaces containing a fluid-like material similar to that often present within the lumen of the cleft. SEM results easily reveal that the submarginal spaces are actually continuous with the complex labyrinthic pituitary system of anastomotic cavities pervading the gland. Such a labyrinth, which was assumed also to be continuous with the lumina of pituitary follicles (Vila-Porcile 1972; Ciocca and Gonzales 1978), seems to have a direct connection with the lumen of the cleft in correspondance with the openings and/or infoldings frequently occurring on its anterior surface. The distribution of this network of spaces around vessels and glandular cells is very similar, as revealed by SEM, to the pericapillary and intercellular spaces in other endocrine glands (i.e.: corpus luteum: Van Blerkom and Motta 1978; adrenal cortex: Motta et al. 1979) and in organs having and endocrine-like arrangement as do the liver plates (Motta and Porter 1974; Motta 1977).

The analogies between these fluid-filled lacunar systems are worthwhile if it is considered that some of the above glands are not provided with typical lymphatic capillaries (Ottaviani 1953; Harrison 1960; Brauer 1963; Vila-Porcile 1972). Therefore the lacunar spaces may perform a similar function which is to collect blood and tissue filtrates and which in these cases might also be related to the accumulation of secretory products before they are released into the circulatory system. Parallel SEM and TEM results show that numerous non-ciliated cells have a variable amount of microvilli and may possess other surface features such as bulbous protrusions and/or lamellar evaginations. These surface characteristics in the marginal cells lining both sides of the cleft are likely the expression of active transport of fluids.

Similar aspects have been described by SEM in the uterine epithelium – where they have been termed "pinopods" by Enders and Nelson (1973) – (Parr and Parr 1977; Barberini et al. 1978); on the luminal surface of the thyroid during reabsorption of colloid (Ketelbant-Balasse et al. 1973; Nunez et al. 1974); and in the tanycytes lining some ventricular regions (Flament-Durand et al. 1978). The more likely interpretation is that these surface structures are an expression of rapid morphodynamic changes related to active processes of endocytosis (Motta et al. 1977).

TEM observations reveal that the majority of marginal cells of the cleft do not possess the typical features of secretory cells and thus it is unlikely that they may directly contribute to the secretion of the material (colloid) often contained in the cleft. On the basis of the present results it is more logical to conclude that the fluid-like material present in the pituitary cleft is mainly derived from the fluids contained in the lacunar spaces of the pars distalis of the gland. Thus, this material should be regarded as a product arising from the parenchymal cells and blood filtrates, rather than as a secretory product of the marginal cells lining the cleft of the adenohypophysis. Marginal cells by absorbing fluids from the cleft by active endocytosis may however, transport to the pars intermedia material (and hormones) produced in the distal part of the gland and viceversa.

The presence of cilia on many cells of the cleft – which considering their 9+2 tubular pattern, are likely connected to a kynetic function – may serve to facilitate the circulation and subsequent absorption of the fluids in a manner which probably is not different from that performed by the ciliated cells of the ependyma (Mestres 1978).

Further SEM results show that a diverse population of marginal cells line the pituitary cleft. Besides microvillous and ciliated cells already described in earlier TEM reports (Vahna-Perttula and Arstila 1970; Yoshimura et al. 1977; Ciocca and Gonzales 1978) other elements are present which reveal a different size and shape and have a smooth surface with few cilia, scarse microvilli and small blebs. Among these cells also a few appear loosely attached to the marginal layer limiting the lumen of the cleft, or are actually free on its surface. Features, such as smooth areas, blebbing, and lamellar and microvillous evaginations may correspond to continuous dynamic changes occurring on the surface of these cells as an expression of the normal cell cycle (Porter et al. 1973). Other aspects related to apparently desquamated free cells can be envisioned as a process of cellular death (Vahna-Perttula and Arstila 1970; Dingemans and Feltkamp 1972; Ciocca and Gonzales 1978; Ciocca 1980).

The dynamism of these surfaces as suggested by the SEM analysis of the cells lining the pituitary cleft is in agreement with the concept that several marginal and follicular cells of the hypophysis, which have numerous structural similarities (Kagayama et al. 1969; Dingemans and Feltkamp 1972; Vila-Porcile 1972; Yoshimura et al. 1977; Ciocca and Gonzales 1978) and are primitive or undifferentiated elements which, forming a sort of "renewal cell system" (Yoshimura et al. 1977), may play an important role in the mitotic activity of the gland.

In the light of this interpretation it is rather obvious to suggest that the cells provided with a variable amount of cilia and located within the pituitary parenchyma (mainly in the follicles) likely arise from the ciliated elements present in the marginal layer of the cleft.

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