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SCANNING ELECTRON MICROSCOPY OF THE HUMAN THYROID GLAND AND ITS DISORDERS

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Abstract

The characteristic scanning electron microscopic features of the normal thyroid gland, benign thyroid lesions such as nodular (adenomatous) and colloid goitre, adenomas and thyroiditis, and malignant tumors such as papillary carcinoma, follicular carcinoma, anaplastic carcinoma and medullary carcinoma are described.

One or more cilia are present in the center of the follicular surface of almost every epithelial cell in the normal thyroid gland as well as in most goitres. Their number is reduced in adenomas and differentiated carcinomas. Medullary carcinomas and anaplastic carcinomas usually lack cilia.

Variation in distribution and appearance of microvilli seems to be related to functional differences in the normal thyroid and goitres. In neoplastic conditions the abundance of microvilli steadily decreases from ordinary papillary carcinomas to follicular variants of papillary carcinoma and to follicular carcinoma. Most of the cells in medullary carcinoma and anaplastic carcinoma have few or no microvilli.

Benign and neoplastic Hürthle cells have a very characteristic appearance. Distinct, smooth-surfaced cells are interspersed among cells rich in microvilli.

The literature is reviewed. Our own experience from examinations of 264 thyroid specimens is included.

Key Words: Human thyroid gland, scanning electron microscopy, thyroid disorders.

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Introduction

Scanning electron microscopy (SEM) gives information about cellular arrangements and surface topography not easily provided by other techniques. Whereas transmission electron microscopy and immunocytochemistry were soon shown to be of value in the diagnosis of certain thyroid lesions, this has not been the case for scanning electron microscopy.

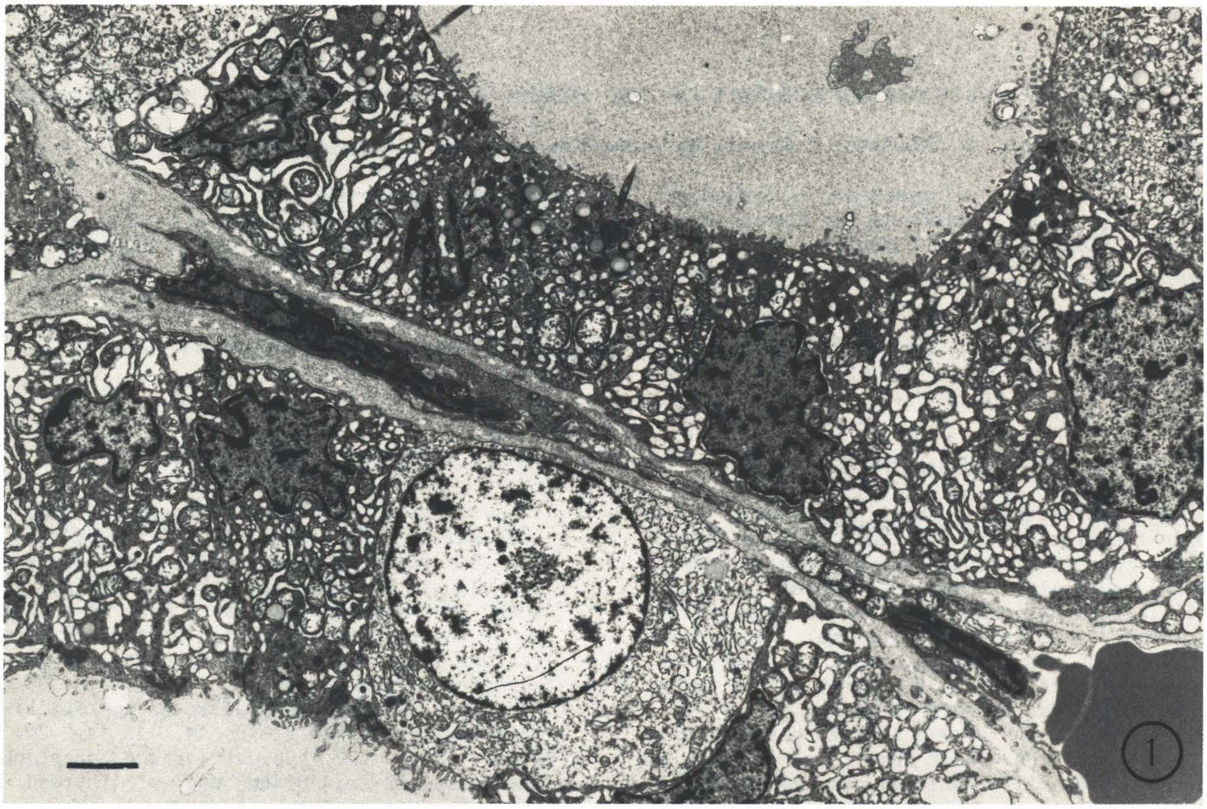
Only a few SEM studies of thyroid lesions have been published (7-10, 14, 16-19, 21). We present now the typical surface topography of the normal thyroid gland and of thyroid disorders. Transmission electron microscopic features will be included when necessary. The findings will be discussed and the literature reviewed.

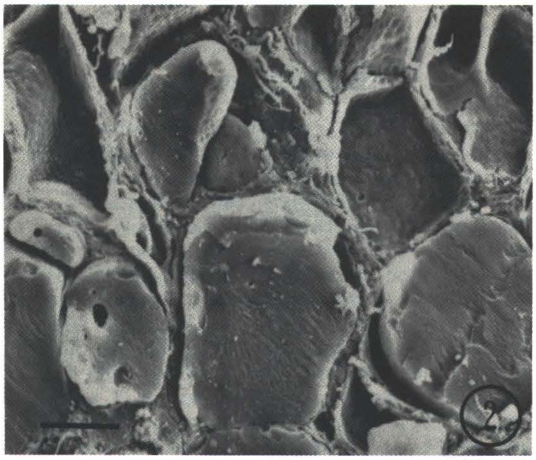
Material and Methods

This study is based on scanning electron microscopic examination of 264 thyroid specimens (45 cases of normal thyroid, 30 goitre, 27 adenoma, 20 Hashimoto's thyroiditis, 8 Grave's disease, 19 Hürthle cell lesions, 82 papillary carcinoma, 19 follicular carcinoma, 5 anaplastic carcinoma and 9 cases of medullary carcinoma).

At the time of surgery, fresh tumor tissue was immediately fixed in a solution of 1% glutaraldehyde and 4% formaldehyde buffered to pH 7.3 in 0.1 M cacodylate buffer (pH 7.3) (11). The specimens were then washed 3 times in the same buffer and postfixed for 1 h in cacodylate-buffered 1% osmium tetroxide. Specimens for transmission electron microscopy were then dehydrated in 70%-90%-96%-absolute alcohol and in propylene oxide for 3 times of 10 minutes each, before embedding in an Epon/Araldite mixture (12). Semithin sections were cut with glass knives, mounted on glass slides, stained with toluidine blue and used for light microscopic orientation. Ultrathin sections were cut with diamond knives from blocks that had well-preserved tissue areas of interest, mounted on 200 mesh copper grids and contrasted with uranyl acetate and lead citrate and examined in a Philips 201 transmission electron microscope.

After fixation, specimens for scanning electron microscopy were dehydrated in graded ethanols and propylene oxide and dried with the





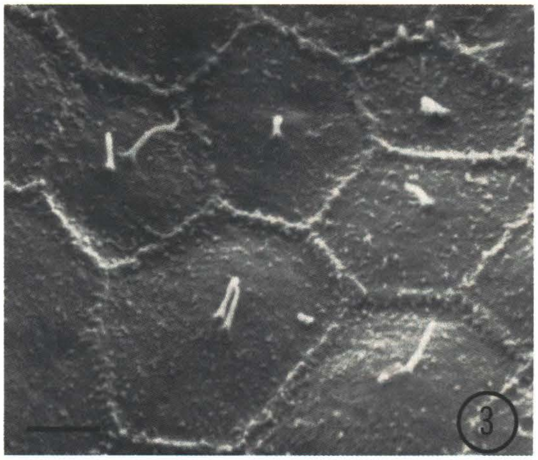


Fig. 1. Normal thyroid. Follicular epithelial cells with dilated, well developed rough endoplasmic reticulum and some lipofuscin bodies. 2 cilia protrude into the follicular lumen. UA/LC (Uranyl acetate and lead citrate). Bar = 3.2 μm.

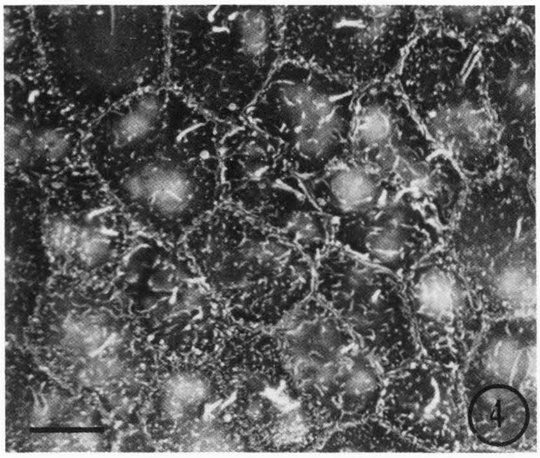
Fig. 2. Normal thyroid. Follicle filled with colloid. SEM. Bar = 64 μm.

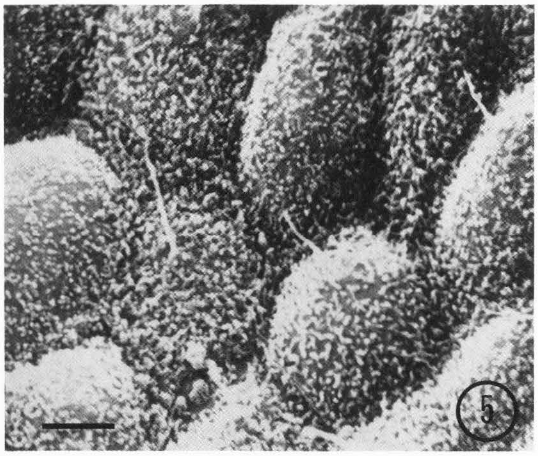
Fig. 3. Normal thyroid. Well preserved follicular epithelial cells recovered from paraffin block. SEM. Bar = 2 μm.

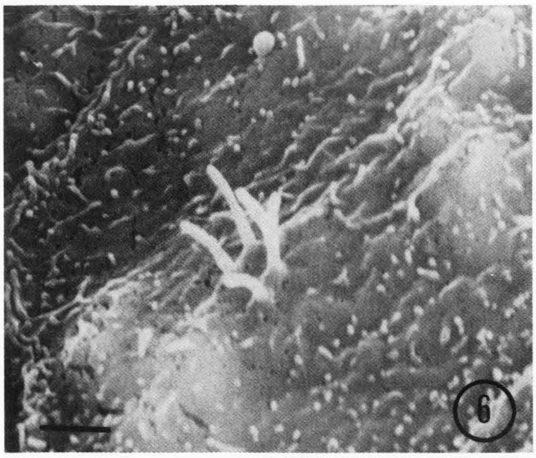
Fig. 4. Normal thyroid. Microvilli are unevenly distributed. The cell borders are distinct and lipofuscin bodies appear as light stained areas. SEM. Bar = 4 μm.

Fig. 5. Normal thyroid. Higher magnification of cells with well developed microvilli. One cilium is present on the surface of several cells in this area. SEM. Bar = 2 μm.

Fig. 6. Normal thyroid. Higher magnification of cells with several cilia. SEM. Bar = 1 μm.







critical point method using CO_2 and a Balzer Critical Point Drier. The specimens were then mounted on stubs, placed under a stereomicroscope for removal of colloid from the follicles with a dental probe (7), and finally coated with vacuum-evaporated gold (density 19.3 g/cc) in a Balzer SCD 030 sputter coater before examination in a Philips SEM 500 scanning electron microscope operating at 25 kV. Pictures were taken with a Polaroid 52 film.

In special cases we used additional material recovered from paraffin blocks and processed as described above.

Results

The Normal Thyroid Gland

If stored colloid is not removed, it fills up the follicles as a homogeneous mass (Figs. 1 and 2). However, it is easily removed, leaving behind a clean, undamaged follicular epithelium layer, even when material recovered from paraffin blocks is used (Fig. 3).

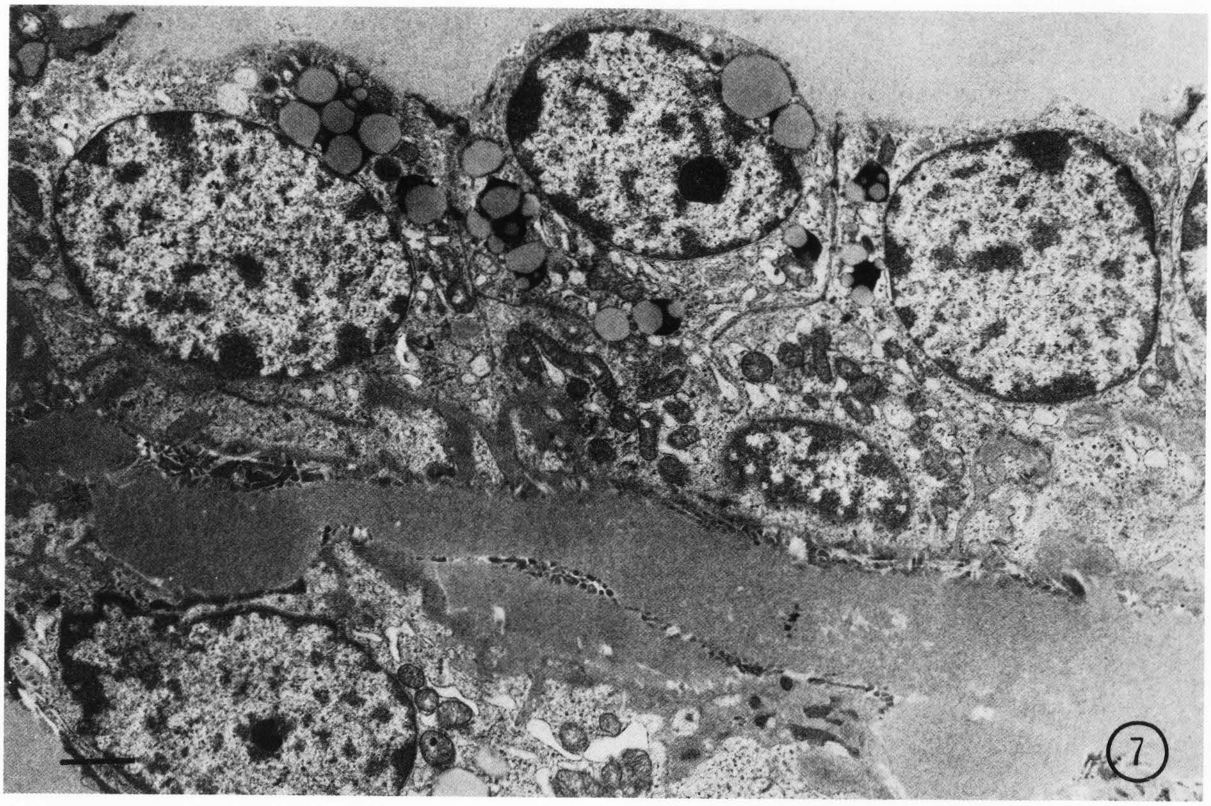
The epithelial cells have polyhedral outlines and usually 4 to 7 slightly raised sides. The central area of the apical cell surface is generally convex, but not always. This area is separated from the raised margins by a concave zone.

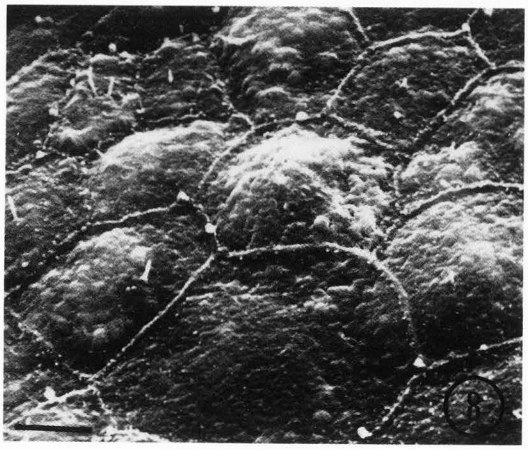
The cell surface has unevenly distributed microvilli, which tend to concentrate along the cell borders (Figs. 4 and 5). The size of microvilli varies with the degree of cellular extension. Small follicles have bigger (up to 1 µm long) and more abundant microvilli than large ones. A semi-quantitative study of the scanning electron micrographs confirmed this subjective impression and showed that there is a significant negative correlation between the density of microvilli and the diameter of the cells (15). Regardless of their length, microvilli have a rather uniform diameter of about 0.1 µm.

Small areas of the cellular surface frequently bulge smoothly into the follicular lumen (Fig. 4). This has been shown to be due to accumulation of lipofuscin residual bodies in the apical parts of the cells (16). Numerous small pits can be seen on the surface if sufficiently high magnification is used (16).

In resting follicles of normal human thyroids we have never seen structures resembling the so-called "lamellipodia" (10). Nevertheless, such cytoplasmic extensions were seen in hyperplastic lesions (Grave's disease and toxic adenoma). These findings support the assumption that lamellipodia (and pseudopods) are involved in colloid phagocytosis and, therefore, prominent in hyperfunctioning lesions (10).

One to several cilia usually protrude into the lumen from the center of the follicular surface of each cell (Figs. 3-6). Cilia may vary in length (up to 6 µm), but are otherwise uniform in their configuration (about 0.2 µm in diameter). When more than one cilium are present, all are of the same size. We have never seen cilia arising from the periphery of the apical surface. Using the tilting device, however, we could demonstrate that they always protrude from the geometric center of the cell





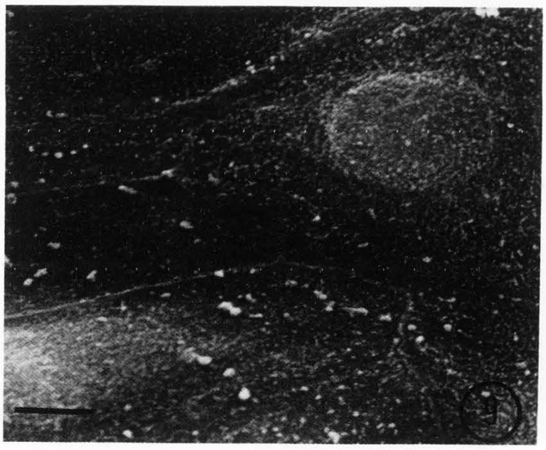


Fig. 7. Colloid goitre. Abundant lipofuscin bodies are present in the follicular epithelium. UA/LC. Bar = 1.6 μm.

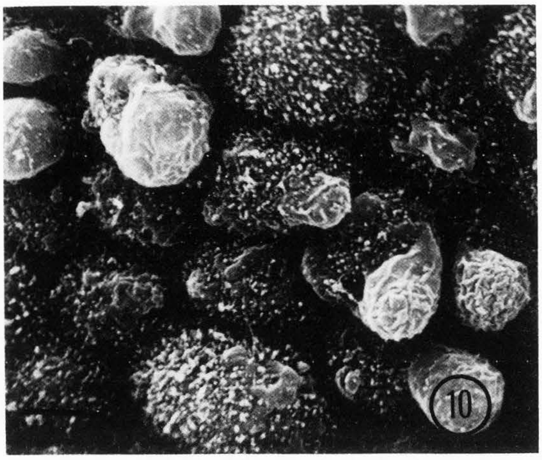
Fig. 8. Colloid goitre. Detail from a larger follicle. Microvilli are absent in this area. The accumulations of lipofuscin bodies protrude as light, slightly irregular areas on the surface. SEM. Bar=4 μm.

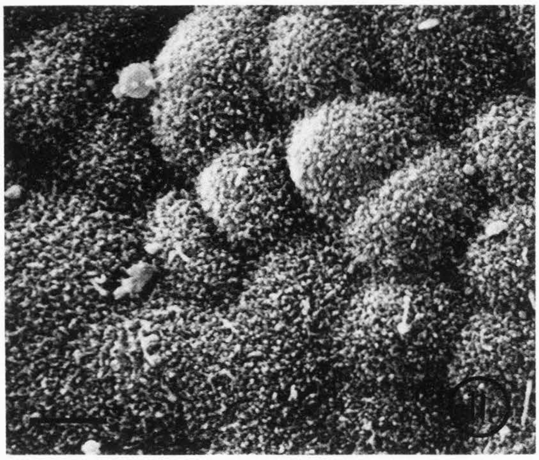
Fig. 9. Colloid goitre. The cells have small, poorly developed microvilli. The surface protrusion is caused by the underlying nucleus. SEM. Bar = 4 μm.

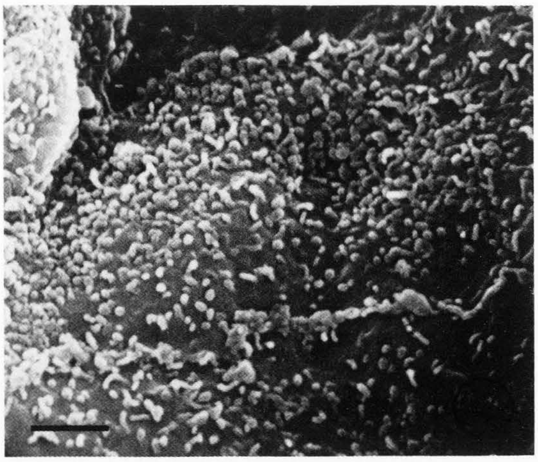
Fig. 10. Colloid goitre. Follicular epithelial cells with blebs of varying size. SEM. Bar = 4 μm.

Fig. 11. Grave's disease. Abundant microvilli are present on the follicular surface. SEM. Bar = 4 μm.

Fig. 12. Grave's disease. Higher magnification reveals that microvilli are mainly knob-like or entangled with neighboring microvilli. SEM. Bar = 2 μm.







surface, even if more than one cilium are present and they do not therefore lie parallel but bend slightly outwards (Fig. 6). In some cases studied by transmission electron microscopy we saw cross-sections of the cilia, which all showed a 9 + 2 microtubular pattern.

Benign Thyroid Lesions

Nodular, adenomatous and colloid goitre

The difference in follicular size is striking. The larger follicles are bordered by large smooth-surfaced cells (Figs. 7-9), whereas the cells in smaller follicles have well-developed microvilli. Cilia are particularly frequent in medium-sized follicles, but tend to disappear either when the cells acquire a squamous-like appearance or when they display a very convex surface. Lipofuscin bodies are present in all follicles and seem to be more abundant than in the normal state (Fig. 8). Blebs, both large and small, are occasionally present (Fig. 10).

Grave's disease

The apical surface is convex or plane and displays abundant microvilli (Fig. 11). In most cases the microvilli are rather short and knob-like (Fig. 12) or entangled with each other. Pseudopod-like structures are prominent in most cases, as has been previously described (10). Small blebs detached from the surface are a frequent finding (Fig. 13). Cilia occur less frequently in Grave's disease than in the normal thyroid. Concurrent use of transmission electron microscopy confirms the extreme complexity of the surface microvilli (Fig. 14) and the abundance of myelinated bodies close to the apical surface (Fig. 15). We believe that both features, as well as the prominence of pseudopod-like projections, are significantly associated with the functional hyperactivity typical for Grave's disease.

Adenomas

The epithelial cells in common follicular adenomas exhibit the same features as in nodular (adenomatous) goitre (Figs. 16, 17, 18). However, the number of cilia is usually smaller (Fig. 18) and cilia may even be absent in large epithelial areas. Accumulations of lipofuscin bodies shining through the cell surface are only rarely encountered, except in the so-called macrofollicular adenomas which have the same scanning electron microscopic appearance as colloid goitre. Toxic adenomas display the same surface features as Grave's disease.

Hashimoto's thyroiditis

The epithelial surface does not have the same rather monotonous appearance as in the normal thyroid (Fig. 19). Cells with a convex smooth surface lie next to cells with varying amounts of microvilli. No cilia or protrusions due to accumulation of lipofuscin bodies are present in some of these cells. In others, a central cilium is present on a rather bald surface. Other follicles appear quite normal. Interfollicular areas are often broadened and contain abundant lymphocytes. Areas with typical Hürthle cell features (see below) are occasionally present.

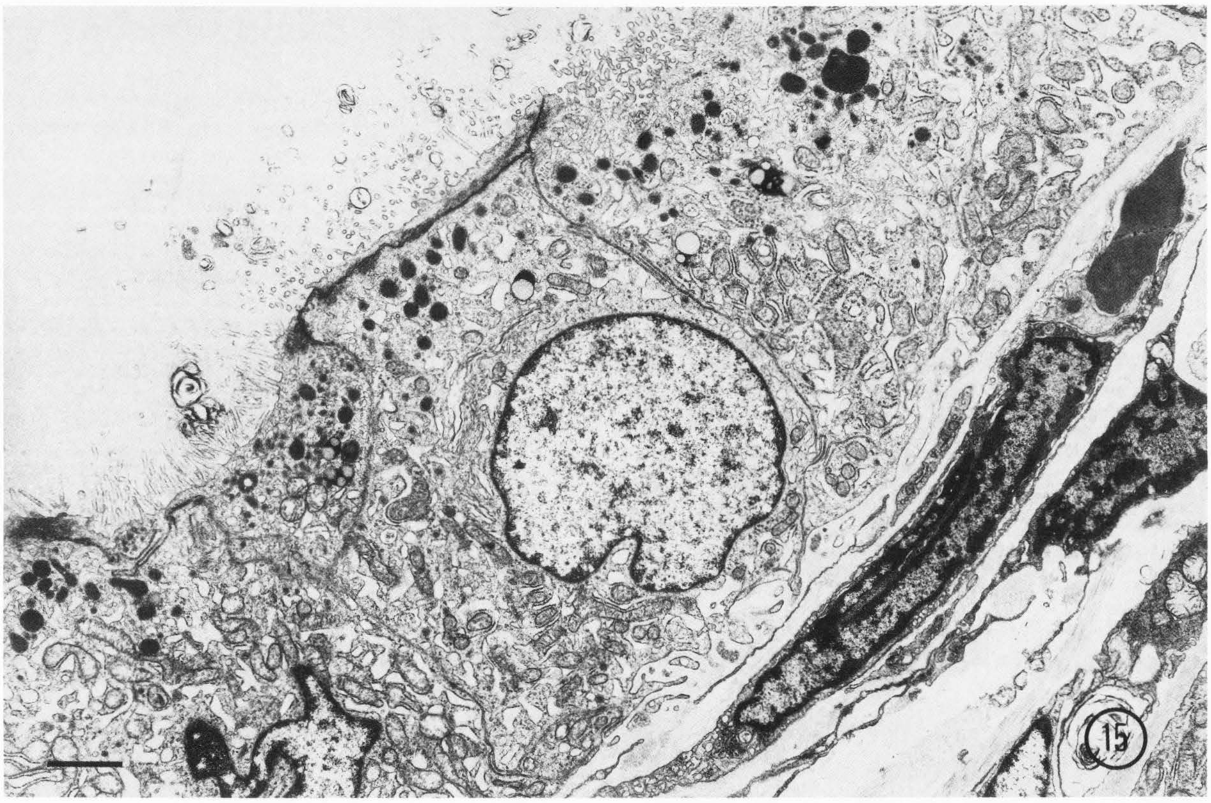


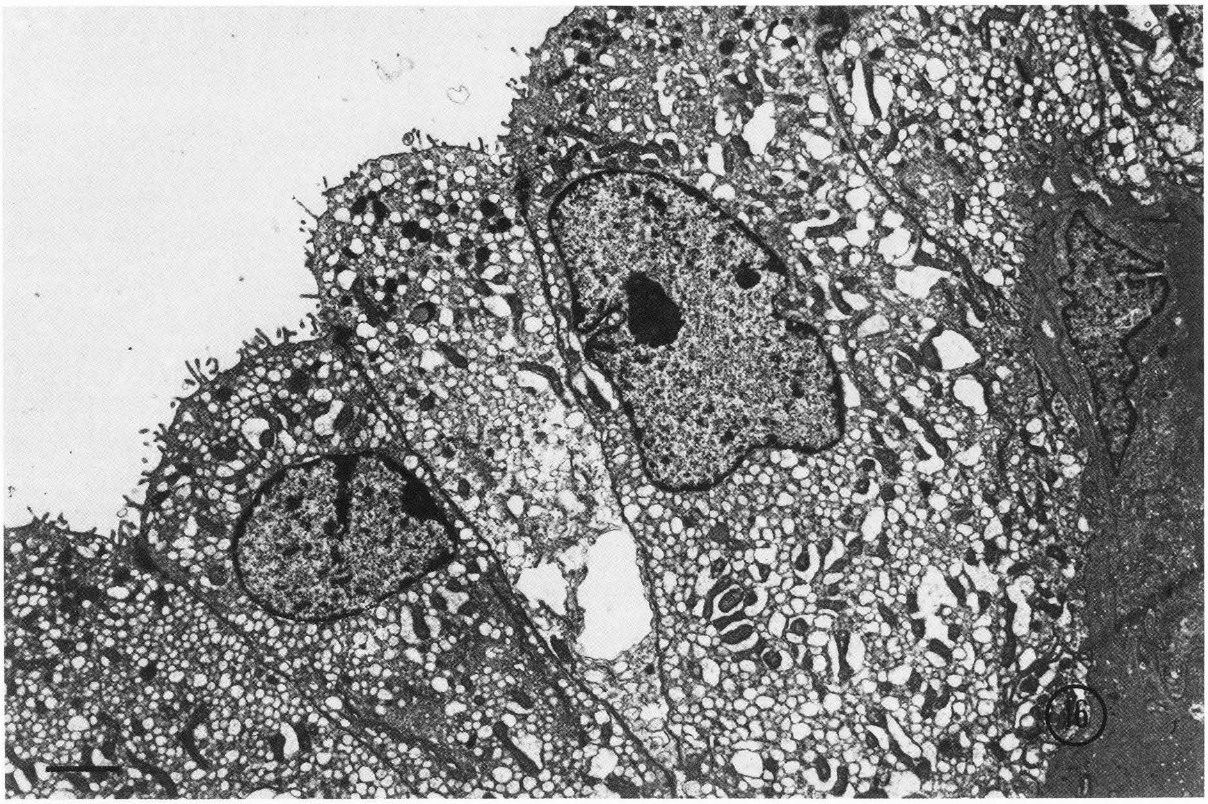
Fig. 13. Grave's disease. Blebs on the surface are frequently present. SEM. Bar = 4 µm.

Fig. 14. Grave's disease. Transmission electron microscopy reveals irregularities in microvilli configurations. UA/LC. Bar = 0.5 µm.

Fig. 15. Grave's disease. Myelinated bodies detached from the apical surface. UA/LC. Bar = 1.6 µm.

Hürthle cell lesions

Neoplastic and non-neoplastic Hürthle cells are similar in appearance (Fig. 20). Smooth-surfaced cells are interspersed among cells that are well equipped with microvilli (Fig. 21). Cells with an intermediate appearance are also present (Fig. 22). This is a very typical morphological feature present in all kinds of Hürthle cell lesions, carcinomas, benign tumors, hyperplastic lesions and even normal thyroid from elderly individuals. Cilia and discrete lipofuscin bodies are present in the "microvilli-rich" cells (Fig. 23) and generally absent in bald cells. Occasionally, however, convex bald cells with a cilium can be observed (Fig. 24). Transmission electron microscopy studies



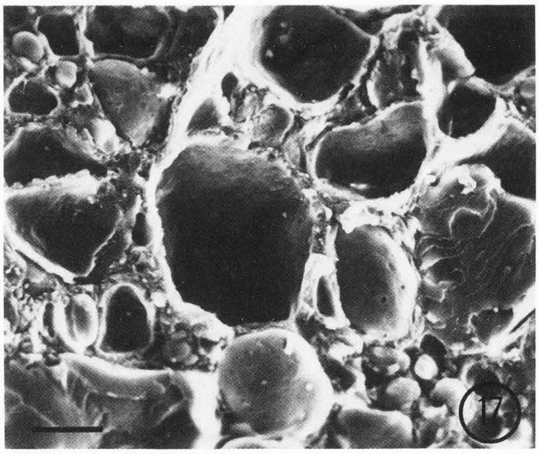


Fig. 16. Follicular adenoma. The cells have irregularly distributed microvilli on the apical surface. UA/LC. Bar = 2.4 μm.

Fig. 17. Follicular adenoma. Survey picture of adenoma with follicles of varying size and some with colloid. SEM. Bar = 4 μm.

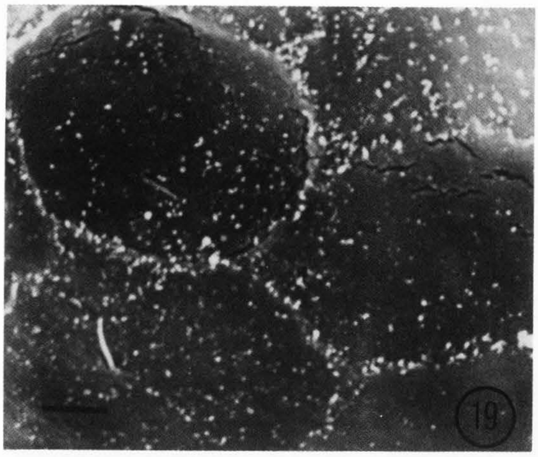
Fig. 18. Follicular adenoma. Higher magnification of cells lining the follicles. An uneven distribution of small microvilli is present and only a small cilium is seen. SEM. Bar = 4 μm.

have revealed that these bald cells do not necessarily correspond to cells crowded with mitochondria.

Malignant Lesions

Papillary carcinoma

Complex papillary structures with varying cell configurations and cell surfaces are prominent (Fig.25). Cells with abundant and long



microvilli (up to 10 μm) and few or no cilia are found next to cells with less developed surface structures (Fig. 26). Lipofuscin bodies are very rare. Psammoma bodies are frequently seen in the papillary stalks.

The follicular variant of papillary carcinoma consists of somewhat concave-surfaced epithelial cells with variations in the number of surface microvilli and cilia (Figs. 27, 28). The cells often have abundant, long microvilli and cilia on the surface more frequently than in common papillary carcinomas (Fig. 29).

Follicular carcinoma

The medium-sized follicles in well-differentiated tumors are covered with smooth-surfaced cells, whereas the small follicles have more abundant microvilli. Usually, one or more cilia are present in the center of each cell surface,

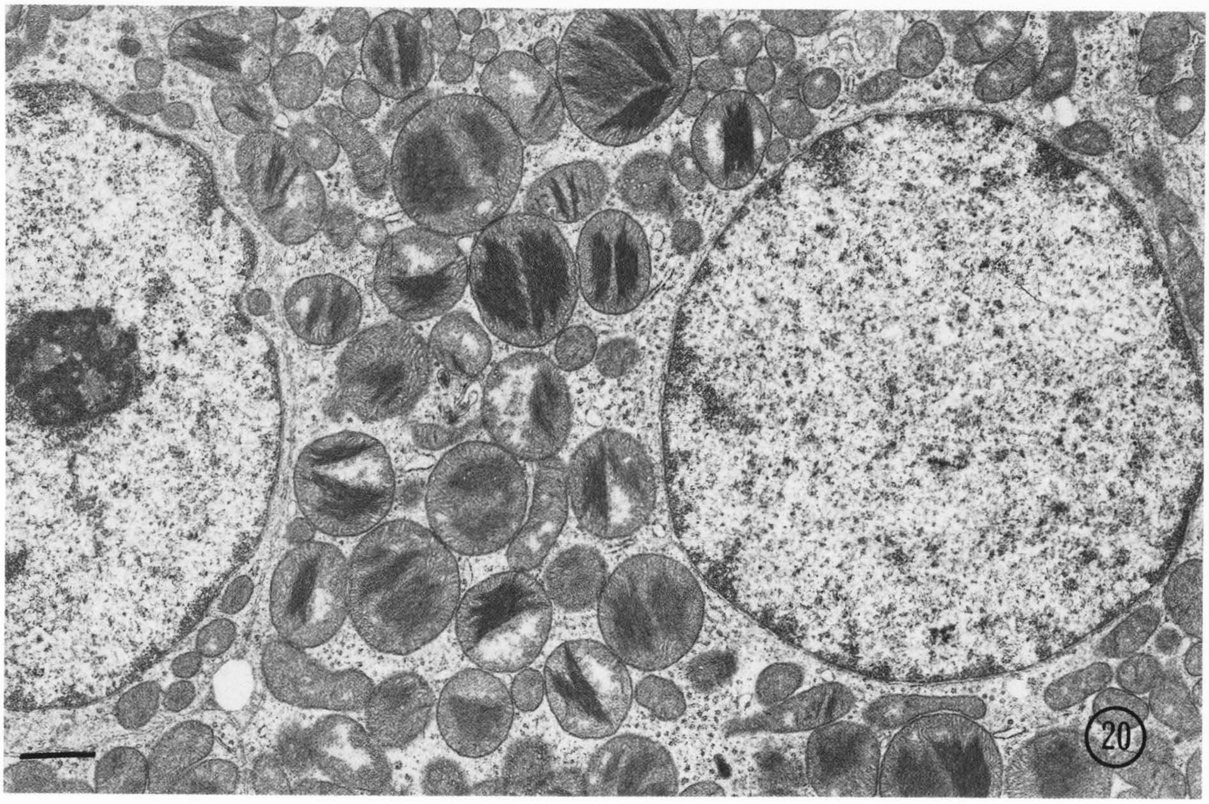


Fig. 19. Hashimoto's thyroiditis. Cells with small microvilli and cilia are seen. SEM. Bar = 2 μm.

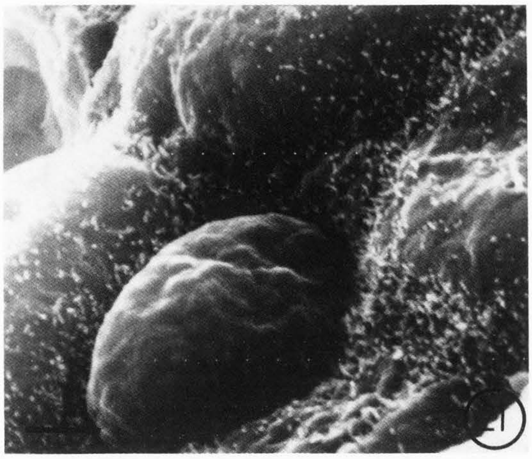
Fig. 20. Hürthle cell follicular adenoma. The cells are crammed with mitochondria. Numerous intramitochondrial filamentous bodies are present. UA/LC. Bar = 1.1 μm.

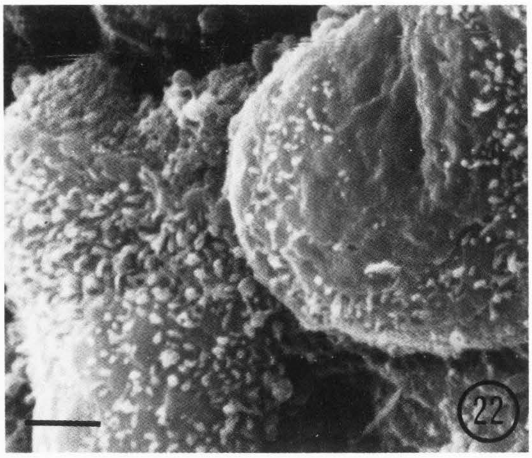
Fig. 21. Hürthle cell follicular adenoma. Smooth surfaced cells lie next to cells with small microvilli. SEM. Bar = 2 μm.

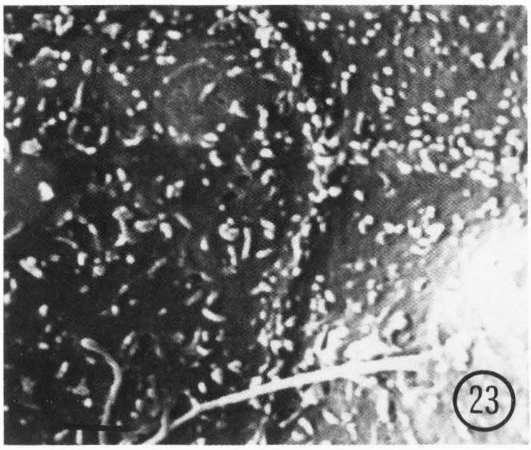
Fig. 22. Hürthle cell follicular carcinoma. A cell with well developed microvilli is close to a cell with a rather smooth surface. SEM. Bar = 2 μm.

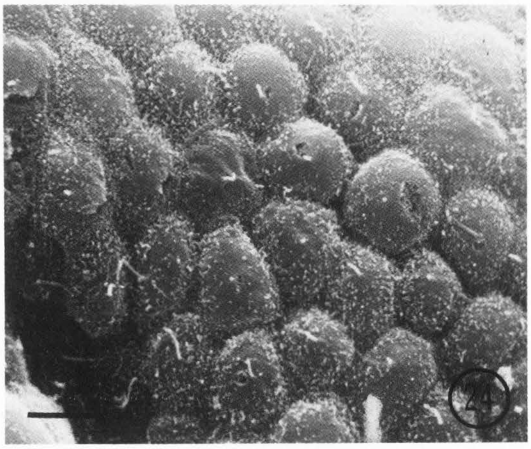
Fig. 23. Hürthle cell follicular adenoma. A long cilium is present in the center of a cell with a lipofuscin body. Small evenly distributed microvilli are present. SEM. Bar = 1 μm.

Fig. 24. Hürthle cell follicular adenoma. Partially smooth-surfaced cells with cilia. SEM. Bar = 4 μm.









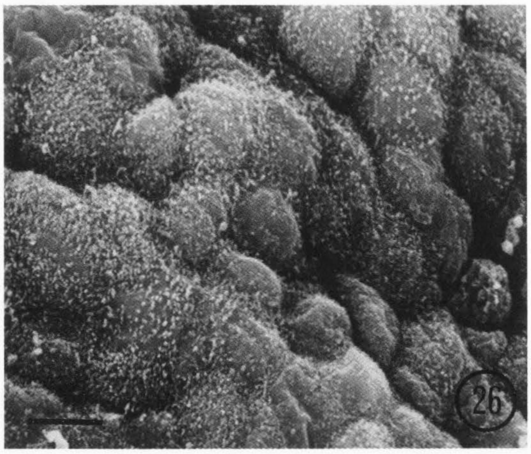
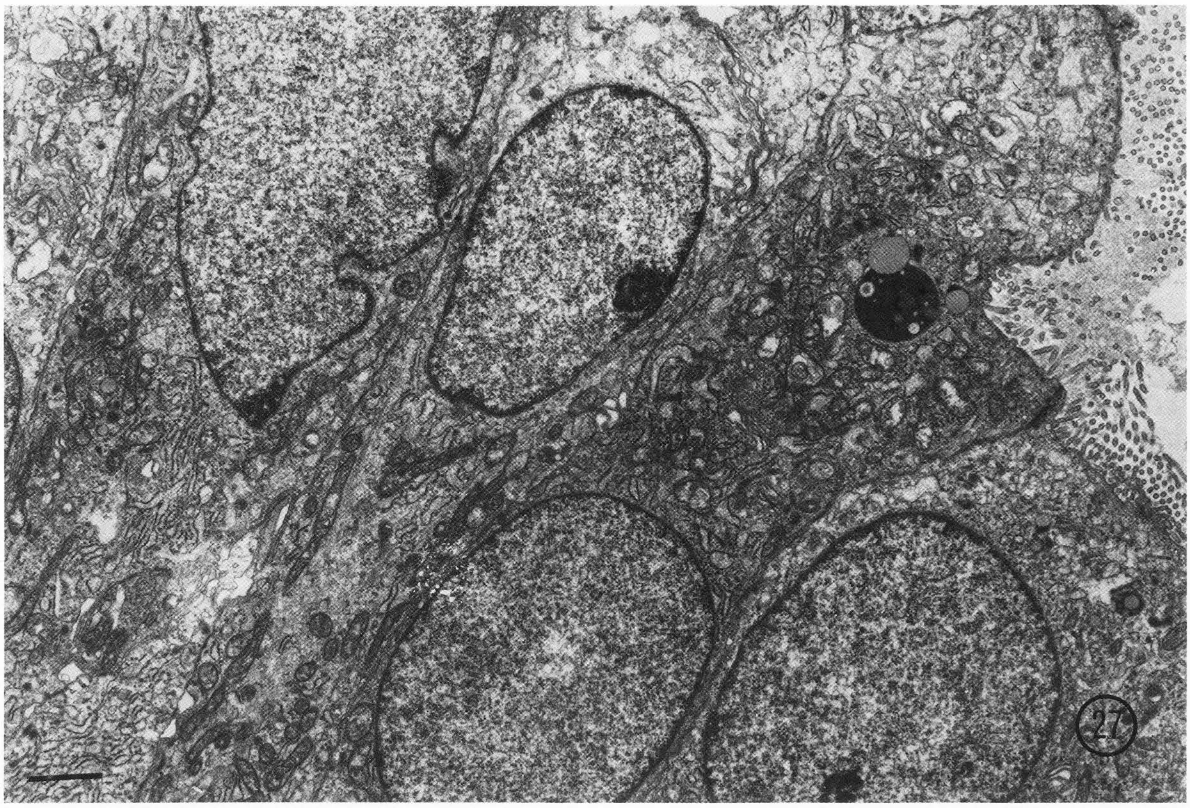
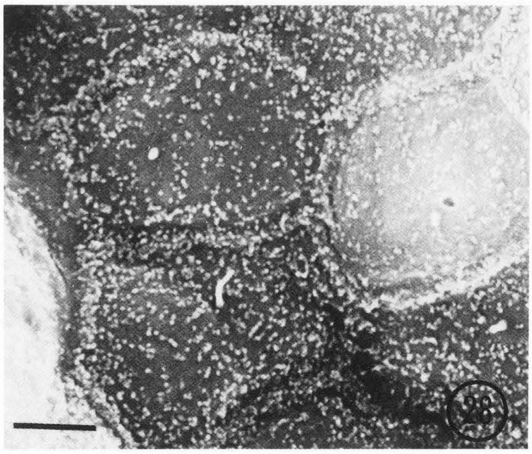


Fig. 25. Papillary carcinoma. Overview picture of papillary structures. SEM Bar = 17 μm.

Fig. 26. Papillary carcinoma. The surface is covered with unevenly distributed microvilli. SEM. Bar = 4 μm.





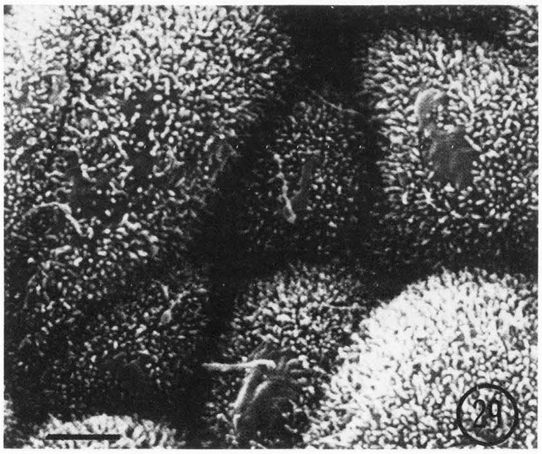


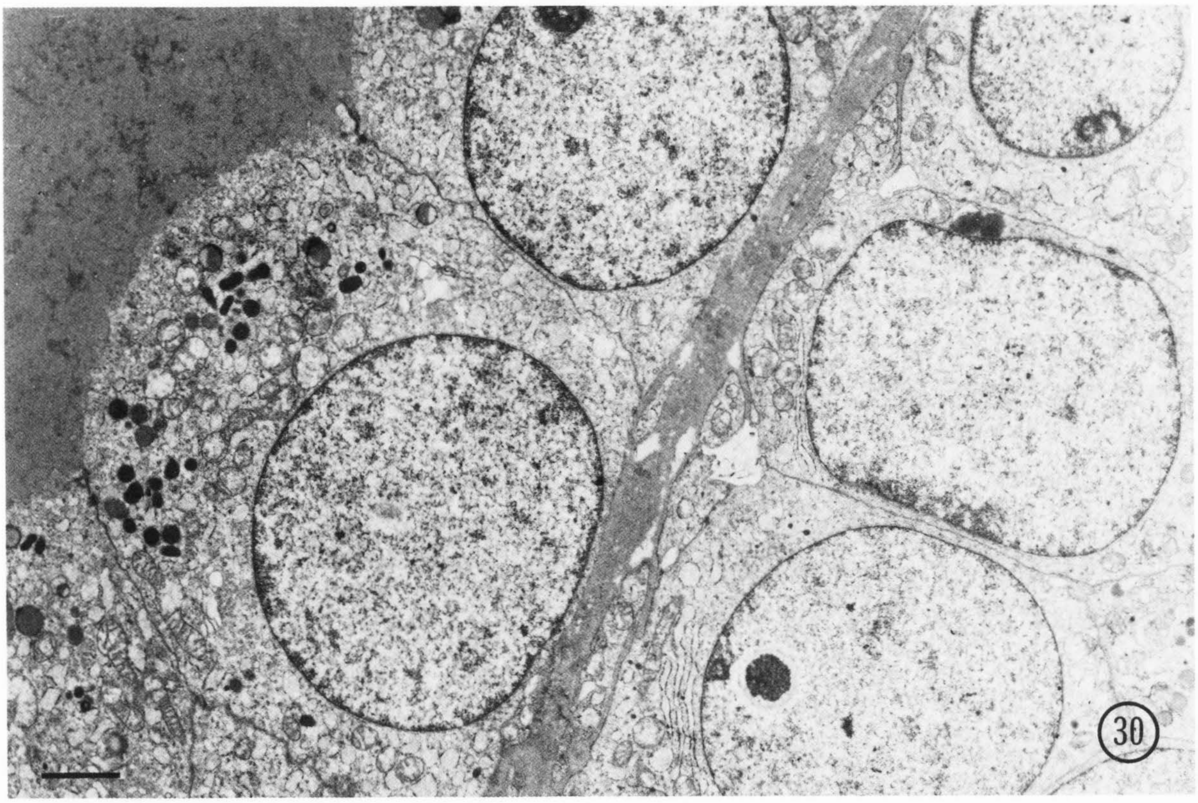
Fig. 27. Papillary carcinoma, follicular variant. The cells are well equipped with microvilli on the surface. UA/LC. Bar = 1.6 μm.

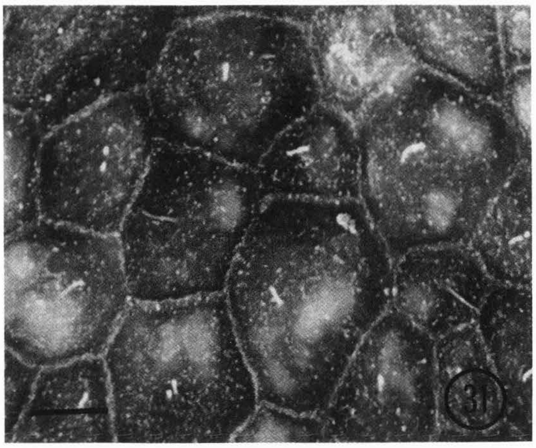
Fig. 28. Papillary carcinoma, follicular variant. Some cells lack cilia on the surface in this area. SEM. Bar = 2 μm.

Fig. 29. Papillary carcinoma, follicular variant. Higher magnification of cells with abundant microvilli. SEM. Bar = 2 μm.

Fig. 30. Follicular carcinoma, well differentiated. The round nuclei have a light stained chromatin and small nucleoli. An accumulation of lipofuscin bodies is present in the apical part of the cytoplasm. UA/LC. Bar = 1.6 μm.

Fig. 31. Follicular carcinoma, well differentiated. Surface of a small follicle. Abundant lipofuscin bodies appear as light stained areas on the surface. One cilium is present on each cell. SEM. Bar = 26 μm.





and rarely, large protrusions due to accumulations of lipofuscin bodies can be seen (Figs. 30, 31).

The follicles of most moderately differentiated follicular carcinomas are too small to be examined by scanning electron microscopy. Whenever they are big enough to be examined, they show more variation in individual cell appearance. Unevenly distributed microvilli and an occasional cilia are the most prominent features. The cilia are usually smaller than those in normal follicles and in well differentiated follicular carcinomas. Lipofuscin bodies are rarely present.

Anaplastic carcinoma

Large and small cells lie in juxtaposition and have no special configuration (Figs. 32, 33, 34). Both sizes are usually well equipped with microvilli but some smooth-surfaced cells are seen. Scattered blebs are present but cilia are absent.

Medullary carcinoma

The tumor cells, which are regular in size, have mainly an irregular surface. In some areas, cells with poorly developed microvilli are present (Fig. 35). Follicular variants of medullary carcinoma of the thyroid usually show the same poorly developed microvilli, but here again the follicles are generally too small to be examined by SEM. Cilia are usually absent.

Discussion

One major obstacle to surface studies of the thyroid gland has been the presence of colloid in the follicles. The easy method of removing colloid from fixed and critical point-dried material has enabled us to study follicles with an unharmed and very clean epithelial surface (7).

The presence of one or more cilia in the very center of the follicular surface of almost every epithelial cell in the normal thyroid gland is a very characteristic feature. In other glandular organs, such as the breast, cilia are not present, and are only very rarely encountered in breast carcinomas (13).

Do cilia then have a function in the thyroid gland? It is not known whether such regularly arranged cilia have any functional significance, e.g., in stirring the colloid to

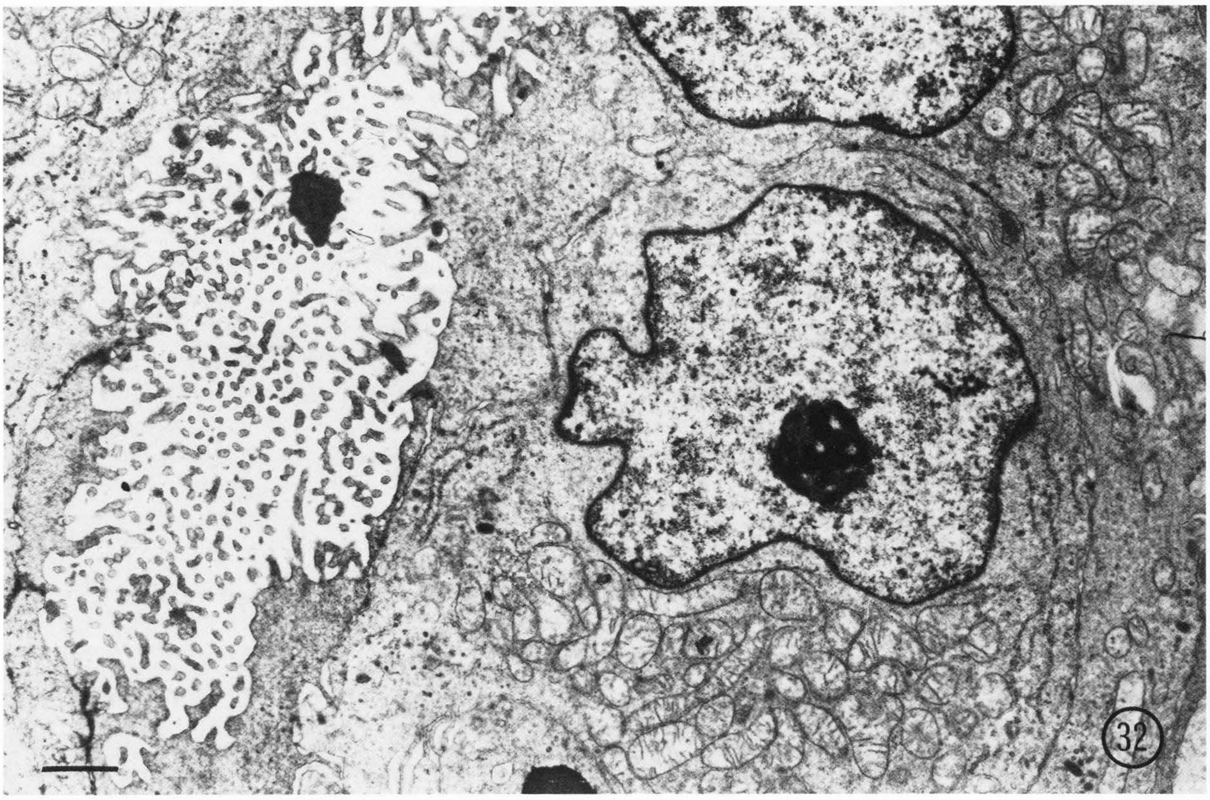


Fig. 32. Anaplastic carcinoma. Tumor cells with irregular nuclei, prominent nucleoli and abundant mitochondria. Well developed microvilli are present on the surface. UA/LC. Bar = 1.1 μm.

Fig. 33. Anaplastic carcinoma. The cells vary in size and surface appearance. Some cells are covered with well developed microvilli, SEM. Bar = 4 μm.

Fig. 34. Anaplastic carcinoma. Higher magnification of cells well equipped with rather uniform microvilli. SEM. Bar = 2 μm.

Fig. 35. Medullary carcinoma. Large tumor cells with an irregular surface. Cilia are not present. SEM. Bar = 12 μm.

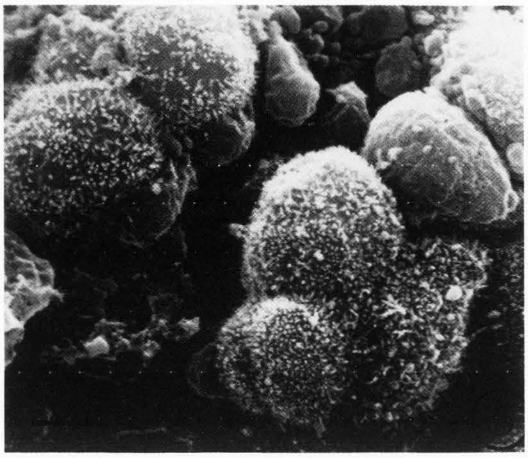
facilitate iodination at the cell apices (8, 16, 22, 23). The aim of our study of several cases of Grave's disease and toxic adenoma was to provide additional support for this hypothesis. Our finding of a normal or reduced number of ciliated cells in these conditions compared to the normal state seems to indicate that cilia do not play a major functional role, at least under these hyperactive conditions.

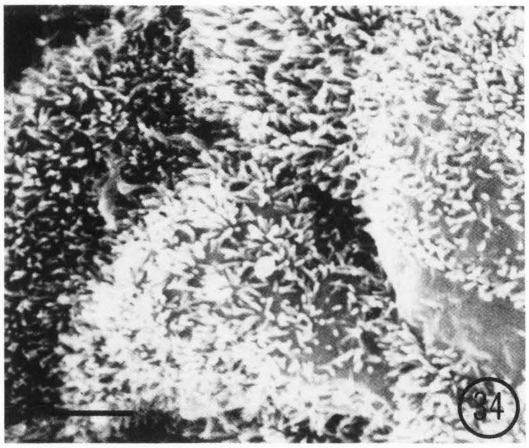
On the other hand, there is some evidence linking cilia to function. First, cilia are not distributed randomly on the cell surface, but always occupy the geometric center of the follicular surface. This also occurs when more than one cilium are present, and indicates that ciliogenesis is a well regulated phenomenon in these lesions. The question is whether the ciliary arrangement is the consequence of a special morphological cellular arrangement or that cilia lead to a special cellular organization. The finding of more abundant ciliated follicular cells in young chickens than in adult fowl favors the latter possibility (4).

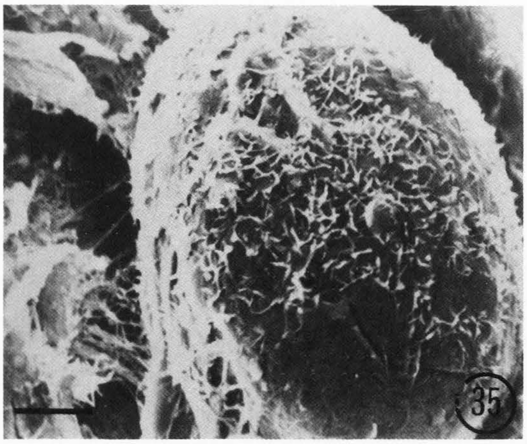
Second, cilia are much more stable on the cellular surface than microvilli. In fact, almost bald thyroid cells may still be equipped with cilia. It is noteworthy that the morphological variation between neighboring cells within the same normal or goitrous follicle, or between cells from different follicles is caused by microvilli, and apparently does not interfere at all with the number, size and configuration of the cilia.

Third and finally, there seems to be a link between the plane or concave shape of the surface of the follicular cells and the presence of cilia. When the cells acquire a more pronounced convex shape, the number of cilia is reduced.

The number of cilia becomes gradually reduced from the amount in the normal thyroid gland, through adenomas, well-differentiated follicular carcinomas, moderately differentiated follicular carcinomas to anaplastic carcinomas. Medullary thyroid carcinomas usually lack a conspicuous follicular arrangement of both cells







and cilia. This may be considered as an additional argument favoring the concept that cilia represent a sign of cellular differentiation. This gradual reduction in number of cilia may also be related to the replicative rate of these disorders. Fonte et al. (3) and Afzelius (1) have proposed that the presence of solitary cilia may reflect a transformation of the mitotic centriole into a ciliary basal body, and thereby prevent further mitotic divisions or be the result of a reduced replicative state.

Distribution and appearance of microvilli is of little help in separating thyroid lesions. The variations observed are probably related to functional differences. It is known that hyperfunctioning non-neoplastic cells have abundant, well-developed microvilli (5, 20), whereas a smooth cell surface is associated with inactive cells (16, 17), but this is not true for neoplasms (8). We have also found that in hyperfunctioning disorders (Grave's disease and toxic adenoma) the follicular surface resembles much more pseudopods or lamellipodia than long and well-defined microvilli. Taking into account that these disorders are endocrinologically very active, a reasonable hypothesis is that this complex, entangled surface pattern does indeed favor an increased surface suitable for hyperactive functions (10).

Papillary carcinomas on the other hand have abundant microvilli in spite of usually being endocrinologically inactive (6, 21). Johannessen and Sobrinho-Simões (8) suggested that the increase in microvilli might be a compensatory effect because of low endocrine function, but it cannot be ruled out that the increase in microvilli is independent of both malignant potential and of function (2, 15).

The ultrastructural appearance of Hürthle cells are the same in benign and malignant lesions (14). The cells are crammed with mitochondria of abnormal structure (14) and have a characteristic appearance by SEM. Distinct, smooth-surfaced cells are interspersed among cells rich in microvilli. Papillary carcinomas composed of Hürthle cells blend with mitochondrion-rich papillary carcinomas and share many of their biological characteristics (20). Foci of Hürthle cells may also be found in mitochondrion-rich papillary carcinomas, thus confirming the assumption that Hürthle cell transformation occurs in a stepwise fashion (20). We have also found that some of the smooth cells do not have the typical Hürthle cell appearance by transmission electron microscopy, thus indicating that both features probably represent different functional aspects of Hürthle cells.

Follicular tumors comprise follicular carcinoma, follicular adenoma, variants of papillary carcinoma and rare variants of medullary carcinoma. These tumors cannot be separated with any confidence by scanning electron microscopy. The number, size, and distribution of microvilli, cilia and lipofuscin residual bodies are all closely related to function and are of little value for diagnostic purposes. Follicular variants of papillary carcinomas have the same cell surface features as the cells in follicular carcinomas. The cells in follicular variants of medullary carcinomas usually lack cilia, but even this is of limited diagnostic importance.

Large surface blebs have previously been reported as a frequently occurring phenomenon in follicular carcinomas. We were not able to confirm this in the present enlarged series. Similar surface blebs were also seen in papillary carcinomas and benign conditions, and probably represent an artefact.

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Discussion with Reviewers

R. L. Hackett: Your observations regarding microvilli are interesting. In other organ systems, for example, the urinary bladder, the suggestion has been made and contested that alterations in microvilli are characteristic as the cell progresses from normal to neoplastic. Would you comment upon this and expand upon your own findings?

Authors: Studies of other glandular organs, for example the breast (ref. no. 16) have revealed that alterations in microvilli occur with malignant development of the cells. The neoplastic cells of intraductal carcinoma of the breast have abundant, thick, long microvilli, with variations in appearance not seen in benign lesions. Similar alterations in microvilli are not seen in malignant thyroid lesions, and thus distribution and appearance of microvilli is of little help in separating thyroid lesions.