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The Ultrastructure of Thyroid in Chronic Autoimmune Thyroiditis

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Die Ultrastruktur der chronischen Autoimmun-Thyreoiditis

Zusammenfassung. 6 Fälle von Autoimmunthyreoiditis (2 Fälle von chronischer asymptomatischer Thyreoiditis, 2 Fälle von Knotenstruma mit herdförmiger Thyreoiditis und 2 Fälle von Hashimoto-Thyreoiditis) werden licht- und elektronenoptisch untersucht. Die ultrastrukturellen Veränderungen stimmen in allen Fällen überein. Die cytologischen Veränderungen in den Follikelzellen machen eine erhöhte Stoffwechselaktivität wahrscheinlich. Als Besonderheit wird das aktive Eindringen von Lymphocyten und Plasmazellen in die Follikelepithelien (Emperipolese) hervorgehoben.

Summary. In an investigation of autoimmune thyroiditis, two cases of chronic asymptomatic thyroiditis, two cases of nodular goitre with focal thyroiditis and two cases of Hashimoto goitre were studied with the electron microscope. The ultrastructural observations were similar in the six cases. Cytological alterations of the follicle cells were found, some of which suggested an increased metabolic activity. Lymphocytes and plasmocytes established close relationships with the thyroid cells: emperipolesis was encountered.

"Chronic thyroiditis" is characterized by the infiltration of the thyroid parenchyma by lymphoplasmatocytic cells, with serologic thyroid antibodies. This disease may appear with or without goitre. Among the goitrous thyroiditis, one may distinguish cases in which the thyroid is nodular and asymetrical; others in which the thyroid is symetrical but firm to lignous. The latter are well-known as Hashimoto's struma (HASHIMOTO, 1912). Besides these goitrous forms, thyroiditis is often found at necropsy in patients who during life had no clinical sign of thyroid disease or goitre and who died from various causes ("chronic asymptomatic thyroiditis") (SIMMONDS, 1923; WEGELIN, 1926; BASTENIE, 1937 and 1944). Some of these glands are hypotrophic and sometimes are difficult to distinguish from the glands with atrophic thyroiditis observed in myxedema (BASTENIE, 1937 and 1944). Besides lymphocytic infiltration, light microscopic studies (HÜRTHLE, 1894; HAMPERL, 1931 and 1936; LENNOX, 1948; BASTENIE, 1937 and 1944) have called attention to changes in the thyroid follicles. The most well known thyroid cellular lesion is the eosinophilic cell of Hürthle, also described as onkocyte or Askanazy cell (1898).

Electron microscopic studies of pathological human thyroids are scarce (BINET et al., 1963; HEIMANN, 1966). Only IRVINE and MUIR (1963) systematically investigated thyroiditis but their work does not come up to the present-day technical

standards. New ultrastructural studies of auto-immune thyroiditis were deemed necessary to establish the correspondance with conventional microscopy and to review the morphological appearances in the light of modern concepts of auto-immunity.

The purpose of the present work was to study:

1. the ultrastructural changes of the thyroid follicle cells and their relation to the changes observed in light microscopy;

2. the relationship between thyroid and inflammatory cells;

3. the possible ultrastructural differences between the different types of chronic thyroiditis.

Material and Methods

As indicated in previous publications (NÈVE et al., 1965 and 1966; BASTENIE et al., 1965, 1967a, b; BONNYNS and BASTENIE, 1967; VANHAELST et al., 1967), since the last six years, in the course of a general investigation on autoimmune thyroiditis, all patients admitted to the department of general medicine of St. Pierre Hospital in Brussels, have been systematically tested for the presence of thyroid antibodies. It was thus possible to select patients admitted without thyroid symptoms, but diagnosed as suffering from chronic asymptomatic thyroiditis. From such patients, two biopsies were performed on two female patients aged respectively 75 and 77 years, during a tracheostomy for acute respiratory failure. Moreover, two women aged 45 and 50 years, suffering from Hashimoto's goitre[1], and two others, 32 and 55 year-old women complaining from irregular nodular and hard swelling of the thyroid underwent a partial thyroidectomy. All the operated patients were euthyroid. This was established by clinical examination and verified by thyroid function-tests. Only the two cases with chronic asymptomatic thyroiditis had received no previous preoperative hormonal treatment. The thyroidin therapy of the four other cases had not been effective. Clinical and laboratory data are summarized in the table. The weight of the thyroid of the 75 year-old woman with chronic asymptomatic thyroiditis was found at necropsy to be 39 g.

Each case was tested for thyroid antibodies by the tanned red blood cell haemagglutiniation and the fluorescence antibody techniques. Antibodies to thyroglobulin and to thyroid cells were detected in every case and the tanned cell titers were above 1:78.125. Thyroid tissue obtained from these six cases was divided in two: the first for electron microscopy; the second fixed in Bouin's fluid, embedded in paraffin, sectioned at 7 μ and stained with haematoxylin-eosin and PAS for routine microscopical studies. The fragments of tissue for electron microscopy were transferred within one minute after excision to a drop of fixative (glutaraldehyde 4,5% in 0,1 M Millonig's buffer (1962) solution at pH 7,4) and divided into small fragments, about 1 mm^3, which were placed in fresh chilled fixative, during four hours. They were rinsed overnight with 0,1 M buffer solution to which 0.54 g glucose per 100 ml of solution had been added, and postfixed during 30 minutes with osmium tetroxyde 2% in glucose Millonig's buffer pH 7.4.

Dehydration took place in rising concentrations of ethanol. The specimens were embedded in Epon according to LUFT (1961). Ultra-thin sections were made with a diamond knife on a LKB Ultrotome. The staining of the sections was carried out with both uranyl acetate and lead citrate (REYNOLDS, 1963) or with KARNOWSKY's method (1961). A Siemens Elmiskop I electron microscope was used. Semi-thin sections, stained with toluidine blue at pH 12, were studied in all cases.

Results

The three above-mentioned varieties of thyroiditis will be separately described. Light microscopic observations will be compared to electron micrographs. These will principally concern zones of inflammation: the changes undergone by the thyroid cells will be described

1. One of these cases has been described in a preliminary communication (NÈVE, 1966).

Table. *Clinical and Laboratory data*

Patients	Reasons for admission	Goitre	Cholesterol (mg-%)	PBI_{127} (γ-%)	I_{131} captation	Thyroidal histologic diagnosis
1. L. S., 75 years	Cerebral stroke atrial fibrillation bronchorrea	none	275	6,1	—	Asymptomatic thyroiditis
2. D. M., 77 years	Cerebral stroke heart failure bronchorrea	none	270	5,9	—	Asymptomatic thyroiditis
3. V. G., 32 years	Dysharmonious goitre	hard nodular goitre since 15 years	183	6,2	41% after 6 hrs. 42% after 24 hrs.	Nodular goitre with focal thyroiditis
4. C. J., 55 years	Disharmonius goitre compressing trachea	nodular goitre since 18 years	196	6,7	Iodine impregnation	Nodular goitre with focal thyroiditis
5. V. A., 45 years	Diffuse goitre compressing trachea	diffuse and hard swelling since 14 years	222	3,0	24% after 6 hrs. 40% after 24 hrs.	Hashimoto goitre
6. G. M., 50 years *50 years*	Dysharmonious goitre compressing trachea	diffuse but unequal swelling since 1,5 year	250	15	25% after 6 hrs. 35% after 24 hrs.	Hashimoto goitre

first; the nature of the inflammatory cells and their relationships with the follicle cells will be studied next. The changes will be compared with the ultrastructural appearance of the normal human thyroid previously described (NOSEDA, 1954; NÈVE, 1965b; HEIMANN, 1966).

Chronic Asymptomatic Thyroiditis

Light Microscopy. Light microscopy revealed a pronounced heterogeneity. Large areas appeared quite normal with follicles of normal size. Other regions were occupied by an inflammatory reaction. In these zones, the size of the follicles was often reduced and the quantity of colloid decreased. The follicles were separated by bundles of connective tissue with numerous inflammatory cells. The follicular conformation was usually preserved, but the follicle cells were generally modified. The cells looked swollen and often polyhedral. They were characterized by a large, finely, granular, eosinophilic cytoplasm. The nuclei were usually large and irregular, sometimes pyknotic. In some zones, such eosinophilic cells had lost their follicular disposition and were scattered in clusters throughout the gland. Besides these granular eosinophilic cells, careful examination revealed some clear eosinophilic cells with non-granular cytoplasm. They were less numerous than the granular eosinophilic cells. Multi-nucleated cells were sporadically encountered.

Electron Microscopy. The electron microscopical observations confirmed the normal appearance of extensive areas contrasting with zones modified by an inflammatory infiltration.

a) Normal areas: In normal appearing areas, the general organization and the structure of the follicle cells were similar to those of the normal human thyroid. Sometimes, the ergastoplasmic cisternae appeared somewhat distended.

b) Areas with inflammatory infiltration: Even in areas with inflammatory infiltration, the follicular structure was usually maintained. Whatever the types of alterations of the thyroid cells, the intercellular spaces of the cells in follicular arrangements were always closed at their apex by a typical junctional complex (ROBERTSON, 1959; FARQUHAR and PALADE, 1963) and a normal basement membrane always limited the whole follicle without interruption. The follicles were rather small and the interfollicular spaces varied in width from a few hundred Å to several μ. Such spaces were crowded by inflammatory cells and connective tissue. In some areas, clusters of altered thyroid cells were scattered throughout the inflammatory infiltration. In the connective tissue cellular debris were sometimes encountered. The appearance of cells lying in close relation to each other or even of cells within the same follicles might vary considerably.

I. Epithelial Changes

First Type of Abnormal Follicle Cells. Some follicle cells were characterized by an important dilation of the ergastoplasmic cisternae (Fig. 1). The cells had a normal intrafollicular localization: they were usually columnar, placed side by side. The microvilli were sometimes longer than usual. The rounded or oval nucleus was situated in the basal part of the cell. Its morphology and its nuclear membranes were normal. The mitochondria occupied no particular location. They maintained their intimate topographical relationships to the endoplasmic reticulum. The shape of the mitochondria varied: some were elongated and branched

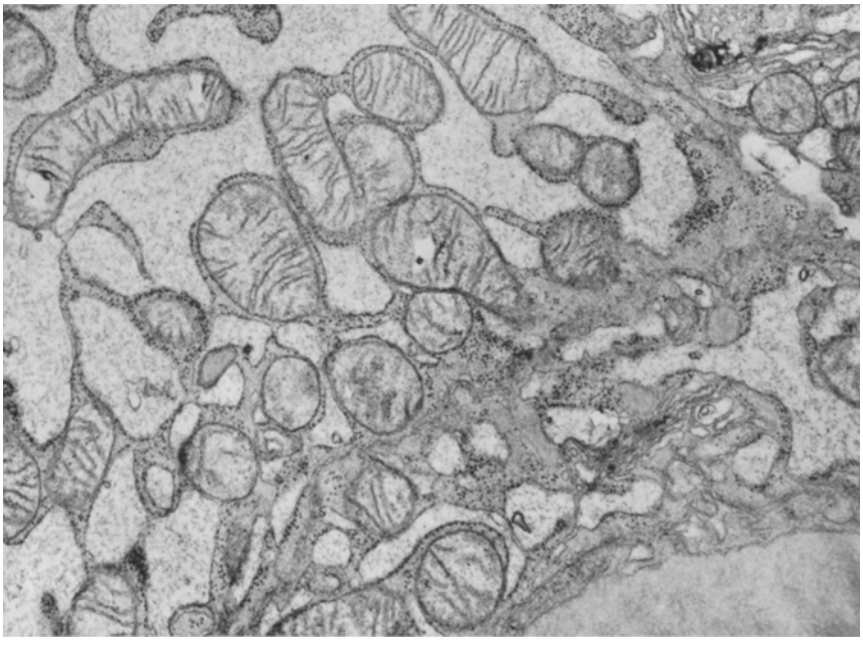


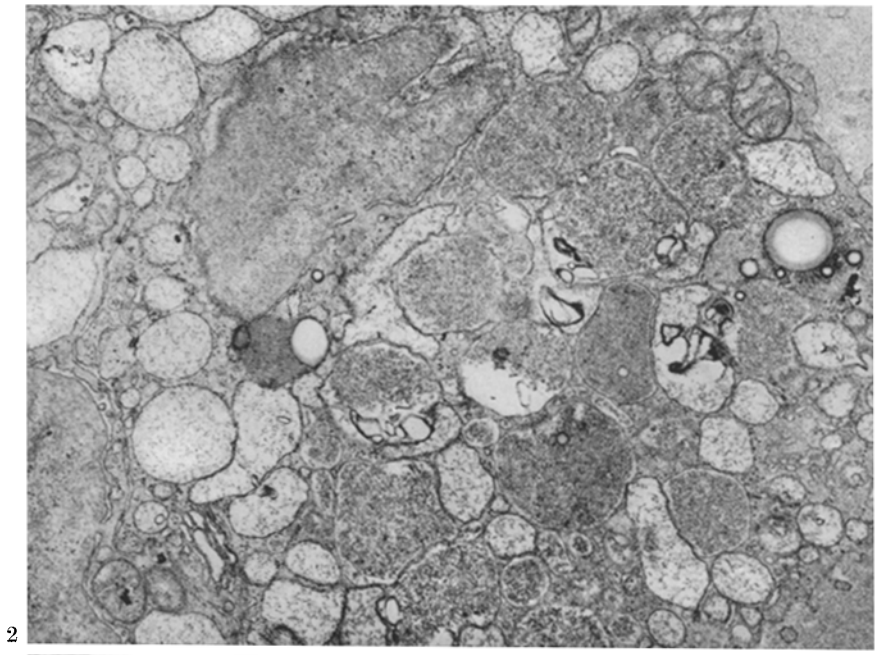
Fig. 1. Dilated ergastoplasmic cisternae characterizing some type of cellular alterations in chronic thyroiditis: here, nodular goitre with focal thyroiditis. 16000 ×

at one end, others were curved. They were generally swollen with stretched cristae. The endoplasmic reticulum was dilated: numerous small round cisternae or large irregular-shaped cisternae occupied large cytoplasmic areas. They contained a finely granular and sometimes filamentous material of low density. The ribosomes were numerous: they were connected with alphacytomembranes or were free in the cytoplasm. Such free ribosomes were sometimes gathered as polysomes containing 3—12 ribosomes. The Golgi apparatus had a great size.

Structures[2] interpreted as phagolysosomes or cytolysosomes, dense bodies and colloid droplets, were scattered throughout the apical zone of the cell. This zone was sometimes occupied by large, more or less dense, rounded inclusions similar to large colloid droplets (Fig. 2).

Second Type of Abnormal Follicle Cells. The number, the shape and the structure of mitochondria characterized some other follicle cells (Fig. 3a). These might be found either in follicles with structural polarization or gathered in compact clusters without follicular lumen, and surrounded by inflammatory tissue. The intercellular spaces and their microvilli were normal. A great number of mitochondria was distributed throughout the whole cytoplasm: in some cytoplasmic areas, they were the only visible organelles. Their shape was very variable, but greatly elongated mitochondria dominated the picture.

2. The identification of some cytoplasmic "droplets" is difficult without histochemical or autoradiographical methods. It is often impossible to determine whether a certain formation should be designated as a colloid droplet or a lysosome. Therefore identification has been done by referring to the publications of DE DUVE (1963), STRAUS (1963) and GORDON et al. (1965).



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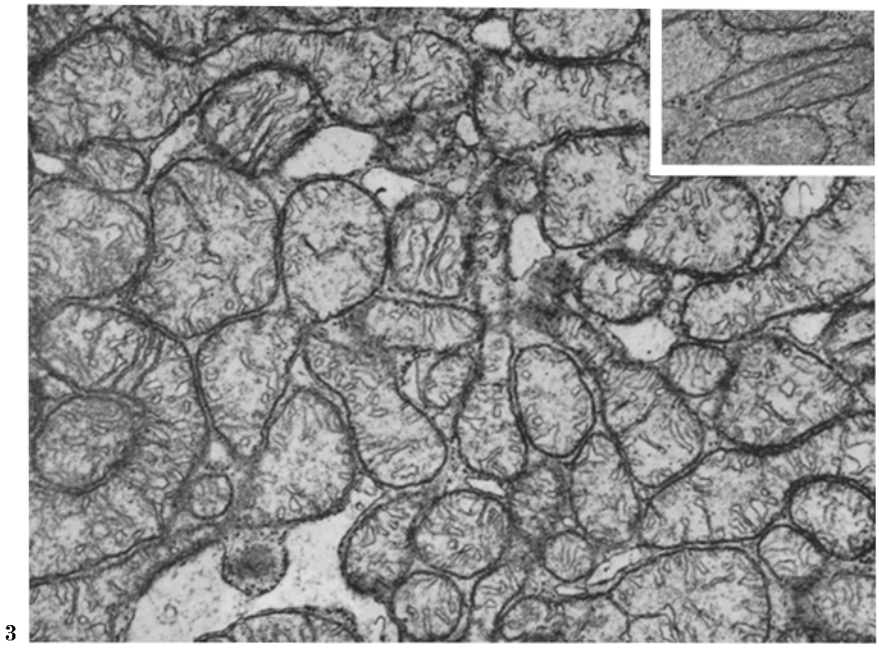

b

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a

Fig. 2. Section through the apical half of a follicle cell displaying numerous rounded inclusions interpreted as colloid droplets. Lipid inclusions and dense bodies interpreted as cytolysosomes are seen. 16,000 ×

Fig. 3. a) Type of mitochondrion rich cells encountered in chronic asymptomatic thyroiditis (here), Hashimoto's goitres and nodular goitres with focal thyroiditis. 18,500 ×

They appeared usually swollen. The inner membranes were most often oriented at right angles to the long axis of the mitochondria. Occasionnaly, the inner membranes tended to run longitudinally (Fig. 3b). No dense granule was observed in the matrix of these mitochondria. The Golgi apparatus was poorly developed. The ergastoplasm appeared relatively reduced: the ergastoplasmic membranes had lost their association with the mitochondria. Some dense bodies were seen here and there. The nuclear volume was normal, nuclei frequently had an indented and wavy outline. The nuclear membranes were separated by a wider space than usually. The outline of some nuclei was very convoluted and some deep depressions of the membranes were occupied by free ribosomes or mitochondria.

Third Type of Abnormal Follicle Cells. A few thyroid cells were characterized by an important modification of their cytoplasm. Such cells were relatively scarce. They could either belong to follicles, or be clustered without colloid lumen. The shape of these cells was variable, but the majority of them had a larger size than normal follicle cells (Fig. 4). The limits between such adjacent altered cells were very tenous but when located in follicles they kept a junctional complex at their apex. The microvilli of the apical membrane were scarce. The nucleus appeared normally structured with a normal volume. The two leaflets of the nuclear membrane were separated by an abnormally wide space. Large homogeneous hyaloplasmic areas occupied the cytoplasm. They were made of homogeneous material, the density and structure of which was comparable to the colloid of the follicle. Such hyaloplasmic areas were sometimes only separated from the colloid lumen by an apical plasmatic membrane. A flattened Golgi apparatus might appear isolated in such hyaloplasmic material. In small zones of the cytoplasm, usual cellular organelles persisted; dilated ergastoplasmic cisternae with ribosomes were associated with swollen mitochondria. Here and there, lipid inclusions and dense bodies were found.

Besides these very differentiated types of changed thyroid cells, numerous cells showed combinations of the three above mentioned cytological modifications.

II. Inflammatory Tissue

The thyroiditis is characterized by the presence of inflammatory cells with connective tissue. These characteristics were found either diffusely or focally according to the variety of thyroiditis. In the regions invaded by bundles of connective tissue mixed with inflammatory cells, it was possible to observe principally plasmocytes and lymphocytes; although a few monocytes, histiocytes and macrophages were also visible. The inflammatory cells were generally localized in the interfollicular space between vessels and basement membrane. Sometimes the cells were observed inside the basement membrane between the follicular cells. They were generally separated from the parenchymatous cells, but particular relationships could exist. First, pseudopods might protrude in close contact with thyroid cells (Fig. 5). Second, plasmocytes or lymphocytes might appear located *inside* parenchymatous cells as in the emperipolesis phenomenon (Fig. 6). The invaded parenchymatous cells showed large homogeneous hyaloplasmic areas in their cytoplasm: no picture suggesting emperipolesis was

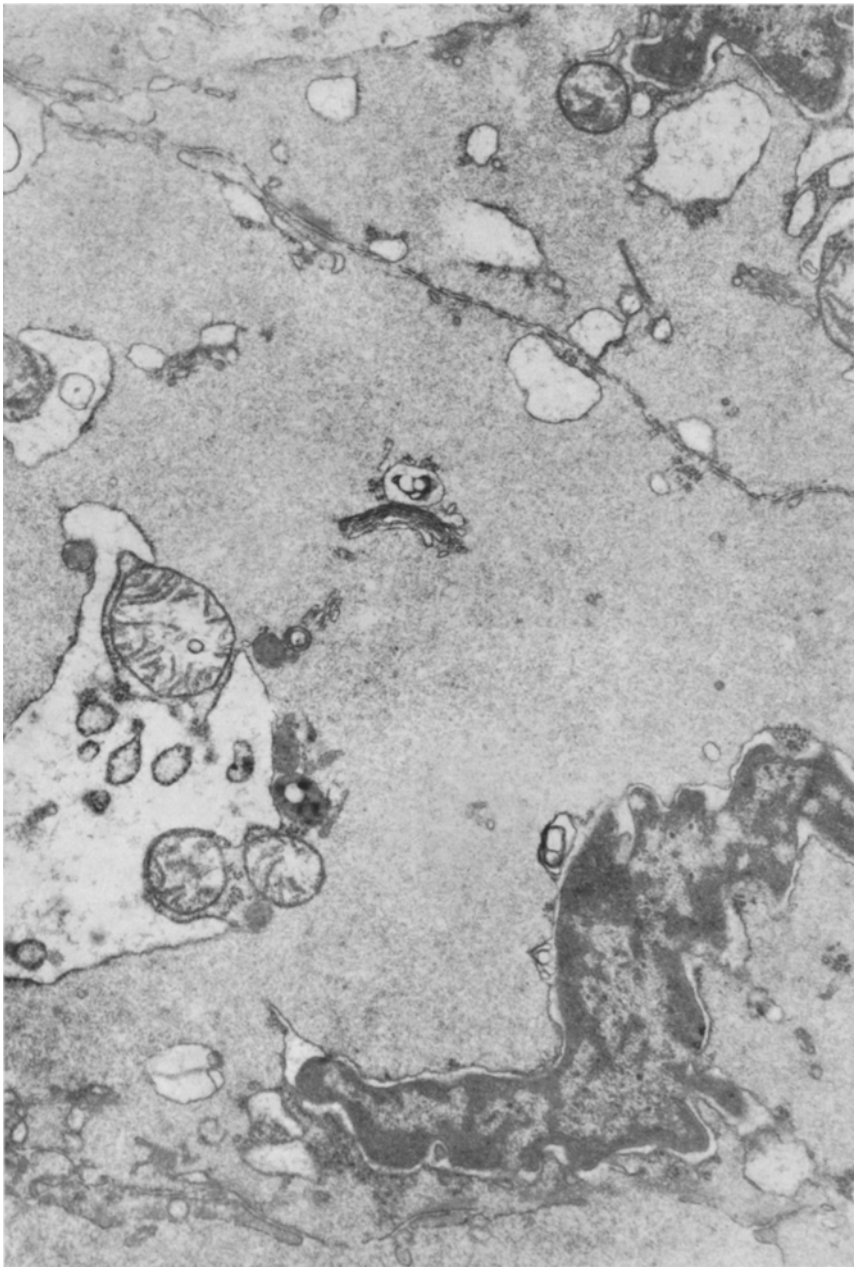

Fig. 4. Nodular goitre with focal thyroiditis: portion of a follicle with large hyaloplasmic areas bordering the colloid lumen. 16,000 ×

found in any other type of thyroid cells. The intracytoplasmic position of the inflammatory cells was indicated by the fact that they were only separated from the cytoplasmic organelles of the host cells by a single unit membrane.

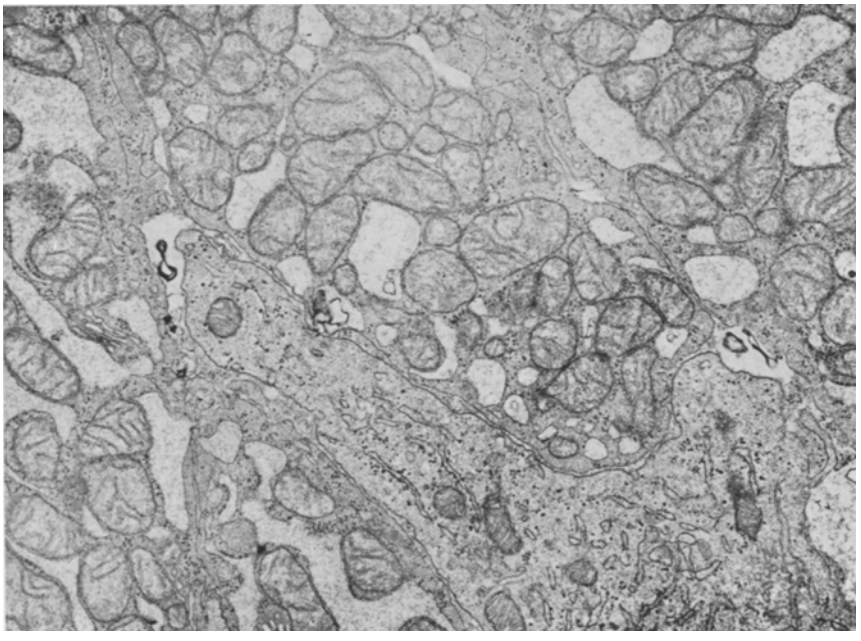

Fig. 5. Cytoplasmic process of an inflammatory cell creeping between adjacent mitochondrion rich cells in Hashimoto's struma. 14,000 ×

Sclerosis varied also condiderably from one region to another. Sometimes, collagen fibrils were very numerous, other times, a rich supply of bundles of collagen fibrils was observed. The fibrocytes with their thin processes were not numerous. Sometimes, extensive areas were only occupied by connective tissue with some cellular debris.

Nodular Goitre With Focal Thyroiditis

Light Microscopy. The two patients with nodular goitre were operated. At macroscopical examination, in both cases the hypertrophied parenchyma was constituted of aggregated irregular rounded nodules. In light microscopy, these nodules appeared formed of large, irregular-shaped follicles with flattened epithelium. These follicles were limited by a bundle of connective tissue and looked like cysts. Between these cysts, the follicles were smaller and more regular: the cells were cuboidal or cylindrical. Their cytoplasm appeared frequently eosinophilic. As in chronic asymptomatic thyroiditis, granular and homogeneous cells with eosinophilic cytoplasm were observed, inflammatory infiltrates were relativelly scarce.

Electron Microscopy. Survey electron micrographs of thyroid cells from large elongated follicles or cysts showed flattened cells with round nuclei and cytoplasmic organelles quite similar to these of the normal human thyroid follicle cells. Outside of the cysts, the follicular cells were usually columnar and, as a rule, the smaller the follicle lumen was, the higher the cell. These follicle cells were generally

diversely modified even in the same follicle. Their shape, nucleus and follicular conformation were normal but cytoplasmic organization was changed. The mitochondria were generally numerous, swollen and rounded. They had an intimate topographical relation to the endoplasmic reticulum. The latter was very well developed, either in the form of numerous small, round cisternae or, more often, in the form of larger irregularly-shaped cisternae. Ribosomes occured in great numbers, as free polysomes or fixed to the alphacytomembranes. The Golgi apparatus was poorly developed. Dense bodies bounded by a unit membrane, phagolysosomes and cytolysosomes were sporadically encountered (Fig. 1). Besides these altered cells with dilated ergastoplasmic cisternae, one observed some mitochondrion rich cells (Fig. 3a) and some cells with extensive homogeneous hyaloplasmic areas (Fig. 4).

These three types of altered cells found in this kind of thyroiditis were quite similar to those described in the chronic asymptomatic thyroiditis. The inflammatory infiltrates were relatively scarce; they were formed by plasmocytes, lymphocytes and phagocytizing cells. The dense connective tissue in which were scattered the inflammatory cells was more abundant than in chronic asymptomatic thyroiditis. The relations between follicle cells and inflammatory cells were similar to these observed in the chronic asymptomatic thyroiditis.

Hashimoto's Struma

Light Microscopy. Contrary to the two above described varieties of thyroiditis, the two Hashimoto's goitres were characterized by an homogeneous pathological appearance. The whole gland was modified by the inflammatory process. Numerous small follicles with cubic epitheloid cells and little colloid were associated with compact epithelial masses. Numerous granular eosinophilic cells were gathered in clusters or had kept their follicular conformation. A careful examination demonstrated some eosinophilic epithelial cells without granulations. Multinucleated eosinophilic cells principally without granules were frequently observed. A considerable lymphoplasmatocytic infiltration with some germinative centers overwhelmed the epithelial follicles. The connective tissue was relatively scarce in comparison with the abundant round cell infiltrate.

Electron Microscopy. Large diffusion of the inflammatory process characterized the disease. The follicular conformation was generally conserved. The follicles were rather small. The shape of the follicle cells was usually cubic or cylindric. Their boundaries and junctional complexes were normal. Some follicle cells appeared normal but many others showed three types of cytoplasmic changes:

1. great abundance of modified mitochondria (Fig. 3),
2. large ergastoplasmic cisternae with free polysomes (Fig. 1),
3. extensive homogeneous hyaloplasmic areas (Fig. 4).

The nuclei of the abnormal cells were often irregular but not larger than normal. A careful examination of the changes undergone by these epithelial cells did not permit one to differentiate them from the changes observed in the chronic asymptomatic thyroiditis and in the nodular goitres with focal thyroiditis. Nevertheless, mitochondrion-rich cells were more frequently encountered. Some thyroid cells showed simultaneously a combination of the three types of changes. Clusters

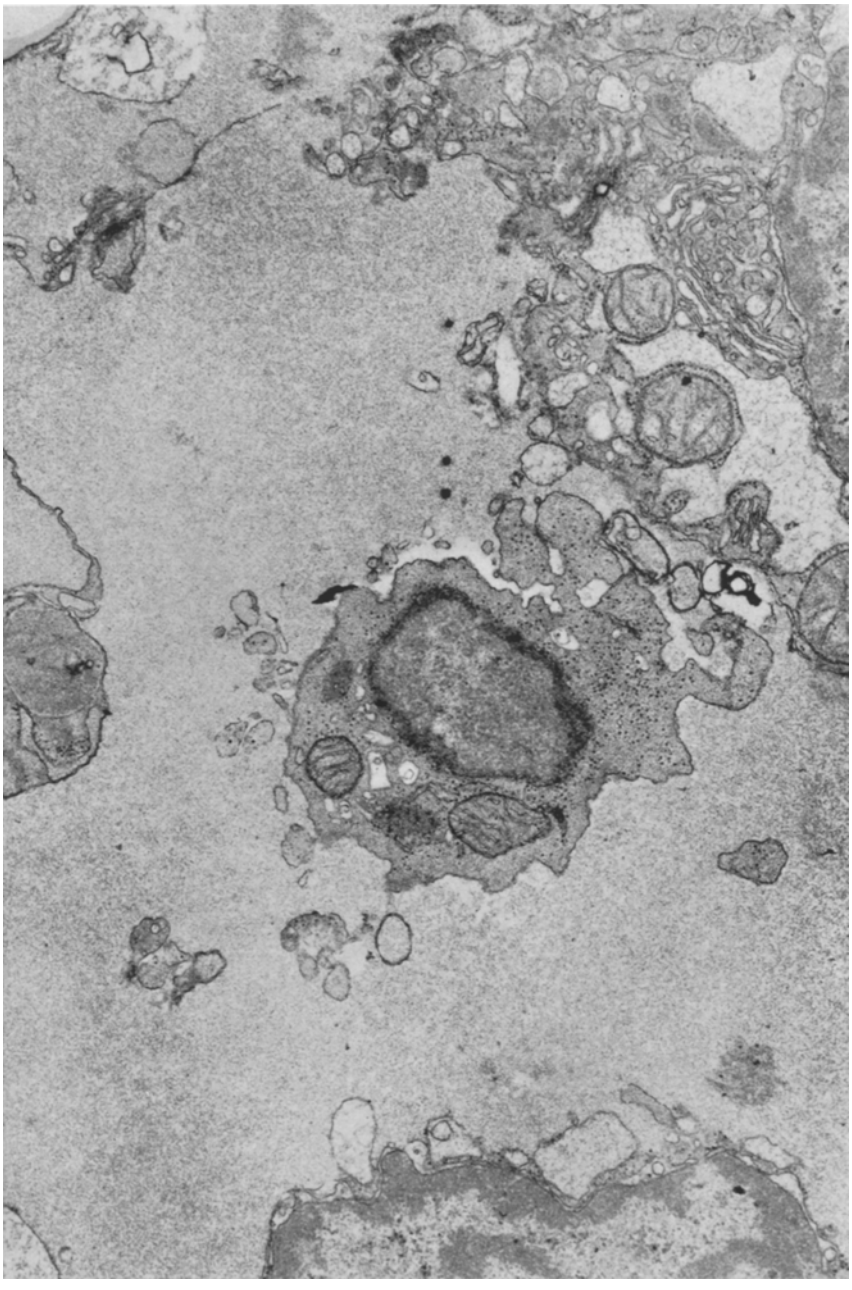

Fig. 6. Characteristic phenomenon of emperipolesis observed in a case of Hashimoto's goitre. 18,000 ×

of mitochondrion-rich cells and of cells with large hyaloplasmic areas were sometimes surrounded by collagen bundles. A heterogeneity of the cellular types might exist between neighboring follicles and also in the same follicle. The in-

flammatory cells were extremely abundant and occupied the spaces between capillaries and follicular basement membranes. Lymphocytes and plasmocytes were inside of or invading the follicles.

As in the cases of chronic asymtomatic thyroiditis the emperipolesis phenomenon was encountered (Fig. 6). The inflammatory cells were also always inside the cytoplasm of epithelial cells which presented the type of alteration characterized by large homogeneous hyaloplasmic areas. The connective tissue seemed less abundant than in the other cases of thyroiditis but its morphology was similar.

Discussion and Conclusions

In spite of the macroscopical differences between the three above investigated variants of thyroiditis, every case was euthyroid and presented circulating thyroid antibodies; moreover, the histological examination confirmed numerous similarities i.e. inflammatory infiltration, connective tissue and epithelial changes. Nevertheless one must remember that the series of thyroiditis with euthyroidism presented here is not representative of chronic thyroiditis considered as a whole. Indeed, the present work does not concern hyperthyroid goitre with thyroiditis, atrophic thyroiditis of myxoedema and so forth. By electronic survey, the epithelial changes of our six cases are represented by three different types of cellular alterations which are encountered in a variable amount in the three different kinds of thyroiditis. The first abnormal cell type presents large ergastoplasmic cisternae with polysomes; the second one, a great abundance of modified mitochondria and the third one, extensive hyaloplasmic areas. A careful examination does not show differences of these abnormal groups according to the variety of thyroiditis. Only the relative quantitative importance of each cellular type varies from one type of thyroiditis to another.

A correspondance can be asserted between the electron microscopic features of these pathological cells and the aspect described with the light microscope. Indeed, as in chronic thyroiditis with goitre and in chronic thyroiditis without hypertrophy, the authors (Hamperl, 1938 and 1950; Bastenie 1937 and 1944; Lennox, 1948) have described in light microscopy similar abnormal epithelial changes: granular cells and clear cells. The granular cells can be assimilated to Hürthle cells, and are easily recognized in routine haematoxylin eosin stains because of their frankly red and uniformly fine granular cytoplasm. Such Hürthle cells have also been observed in salivary glands (Hamperl, 1931; Hübner, 1967), in parathyroids (Roth, 1962), in excised thyrotoxic glands (Heimann, 1966) and other thyroid diseases. The histochemical analysis (Tremblay and Pearse, 1960) or such cells reveals that they contain high amount of oxydative enzymes. It suggests that the *Hürthle cells correspond to the mitochondria-rich cells* described with the electron microscope. Survey electron micrographs of the nuclei of these cells do not confirm their larger size often observed with the light microscope: the indented long and wavy outline of these nuclei explains probably this optical appearance. It is interesting to recall that in Hürthle cells observed in abnormal human thyroids, Harcourt-Webster and Stott (1966) have found high levels of activity of the intramitochondrial enzymes, but none or reduced peroxydase and acid phosphatase activities which concern iodide organification and secretion

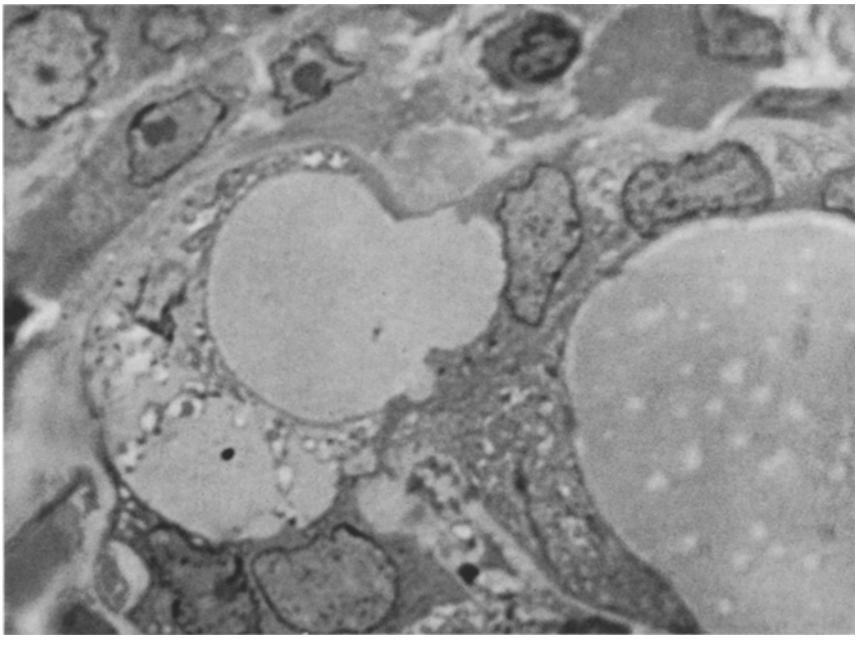

Fig. 7. Semi-thin section through thyroid follicles in a case of Hashimoto's goitre. A clear cell with homogeneous hyaloplasmic areas and partially bordering a colloid lumen is well recognizable. 1,000 ×

respectively. At this time, no definite biochemical explanations of the absence of matrix granules in the mitochondria of the Hürthle cells (HÜBNER and SCHIEFER, 1968) can be given. The absence or reduction of endoplasmic reticulum in the mitochondria-rich cells would indicate that these cells are poorly active in protein synthesis. These findings might be explained as an extreme imbalance between respiratory and other cellular activities.

In light microscopy, besides the Hürthle cells, *clear eosinophilic cells* are observed. They are relatively scarce and their cytoplasm is homogeneously eosinophilic. They are similar to the Langendorff cells observed first in dog and calf thyroids (LANGENDORFF, 1889) and described in man in pathological conditions (BARGMANN, 1939; BASTENIE, 1937 and 1944). They are characterized by a "homogeneous cytoplasm which presents a great affinity for the stains of the colloid" (LANGENDORFF, 1889). The observations of semi-thin sections from Epon embedded material (Fig. 7) stained with methylene blue allow the identification of these Langendorff cells with those with extensive hyaloplasimc areas observed in electron microscopy. When gathered in clusters, the thin intercellular spaces of such cells might lead in light microscopy to an erroneously description of multinucleated cells.

Numerous follicle cells appear normal on electron micrographs and correspond to the non-altered main cells. The few and short microvilli, the normal appearance of the endoplasmic reticulum and the relative scarcity of the mitochondria are ultrastructural features which seem to indicate a relatively low cellular activity.

Correspondance between conventional and electron microscopies cannot easily be established for the cells with large ergastoplasmic vacuoles: indeed, optically some vacuoles appear in the cytoplasm of follicle cells although they may correspond to lipid droplets. It is possible that such type of cell has before been assimilated to one or another type of eosinophilic cells.

It is very difficult to conclude from our morphological study what part is played by the inflammatory cells in the pathogeny of the alterations. Intimate relationships exist between the invading inflammatory cells and the epithelial cells, since some of these are penetrated by lymphocytes or plasmocytes. Because in the present work, all the epithelial cells undergoing emperipolesis present large hyaloplasmic areas with scarce endoplasmic reticulum, different explanations may be proposed. The inflammatory cell may attack and damage the epithelial cell and induces these alterations, or the already deteriorated thyroid cells may become specifically a target for the inflammatory cell. The basic issue has not yet been resolved as to whether the close relationships between the inflammatory and thyroid cells are the consequence of an alteration of the thyroid itself or whether the presence of antibodies and of inflammatory cells denotes an abnormal basic mechanism of immunity. LING et al. (1965) concluded from their experiments that the Hashimoto thyroid cells might be predisposed to invasion by inflammatory cells. Until now, all the experimental works have failed to demonstrate a pathogenic role of the circulating humoral antibodies.

An other explanation may be considered. There is some evidence that the alterations of the epithelium are related to an abnormal stimulation by thyrotropin or thyrotropin-like substance (LINDSAY, 1964). Dilated ergastoplasmic cisternae similar to those observed here have been experimentally produced after acute and repeated thyrotropin stimulation of dog thyroids (personal observations). Moreover in thyroiditis, some cells present at their apex numerous rounded inclusions similar to colloid droplets aggregates observed in dog thyroids two hours after stimulation. These aspects therefore suggest a high cellular activity. Such a thyrotropin stimulation may exist here since an elevated serological thyrotropin level has been described in some cases of chronic asymptomatic thyroiditis (BONNYNS and BASTENIE, 1967).

Whatever the pathogeny of the chronic thyroiditis may be, identical lesions have been observed in the six present cases; generalized in the Hashimoto goitres, the lesions are more focal in the two cases of chronic asymptomatic thyroiditis and in the cases of nodular goitres with focal thyroiditis. Therefore, these three types of chronic thyroiditis appear as variants of the same pathological process.

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