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Ultrastructural Study of the Thyroid in Adult Hypothyroidism*

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Summary. The ultrastructural aspect of the thyroid in acquired hypothyroidism in adult human is quite similar to that described in chronic autoimmune thyroiditis. Only a few follicles persist: most of their cells show an oncocytic transformation. Rare colloid cells are present. A new thyroid cell type characterized by numerous cytoplasmic fibrils is described and its ultimobranchial origin is discussed.

Introduction

Several light microscope studies have described the histological aspect of the thyroid in acquired hypothyroidism in adults (Jaffé, 1928; Bastenie, 1937; Bargmann, 1939; Bastenie, Bonnyns, and Vanhaelst, 1972). Various degrees of fibrosis with lymphoplasmocytic infiltrations of the parenchyma characterize the disease. Recent clinical and immunological investigations have demonstrated that hypothyroidism in the adult is the outcome of an asymptomatic thyroiditis process slowly progressing, after several years, toward parenchyma destruction and consequent hypothyroidism (see literature in Bastenie and Ermans, 1972).

Besides inflammatory infiltrations, there exist cytological changes of the thyroid cells, which appear to be similar to those described in chronic autoimmune thyroiditis i.e. eosinophilia of the cytoplasm characterizing the so-called Hürthle cells or oncocytes (Hürthle, 1894; Bastenie, 1937; Hamperl, 1950). Whereas the ultrastructural nature of these cellular changes has been investigated in Hashimoto's disease and in chronic asymptomatic thyroiditis (Irvine and Muir, 1963; Binet, De Gennes, and Decourt, 1963; Nève, 1966 and 1969; Brandes, Anton, and Orbegoso, 1969; Harris, 1969; Reidbord and Fisher, 1973), until now, no ultrastructural study has been devoted to the thyroid in hypothyroidism. This omission results from the difficulty to obtain biopsy material of the gland in such conditions. The aim of the present paper is to report the fine structure of the thyroid in a case of adult hypothyroidism, where removal of the thyroid was performed just after death.

Clinical Report and Methods

Suffering from angor since several years, this 72 year old woman entered the hospital because of heart failure. Physical examination revealed typical myxoedema confirmed by different laboratory investigations: iodine T_4: 1.4 µg/100 ml; uptake of ^{131}I after 24 hours: 2%. A McKenzie assay of serum thyrotropin performed by Dr. Bonnyns gave 33 mU/100 ml (Normal: 17 mU/100 ml). Soon after admission, the patient died from pneumothorax. The thyroid

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gland was removed immediately after exitus and divided into several fragments fixed either in Bouin's fluid for light microscope examination or in glutaraldehyde for electron microscope study. After embedding in Epon (Luft, 1961), the latter fragments were cut with a diamond knife in serial semithin sections till the moment thyroid follicles and inflammatory infiltrations became recognizable among the fibrosis with the microscope after staining with toluidine blue. In such conditions, the next sections were ultrathin, stained with both uranyl acetate and lead citrate (Reynolds, 1963) and observed with the electron microscope Siemens Elmiskop II.

Results

Light Microscopy

Macroscopically, the thyroid, weighing 30 g, was normal-sized. Histologically, some vestiges of thyroid parenchyma remained inside dense fibrosis occupying the whole gland. The thyroid follicles were small and almost devoid of colloid. The follicular cells were cylindric; most of them showed oncocytic appearance. Lymphoplasmocytic inflammatory cells surrounded the follicles and sometimes infiltrated between adjacent thyroid cells. Several masses of particular tissue were noticed arranged in pluristratified follicles or in cords and made up of cells the cytoplasm of which appeared clear and colored in grey with haematoxylin-eosin.

Electron Microscopy

1. Follicular Cells

Numerous serial semithin sections were necessary before observing areas occupied by thyroid vestiges. In such areas, most of the follicular cells had their cytoplasm filled with swollen mitochondria in which the dense granules were rare. The rough endoplasmic cisternae and the Golgi apparatus were small and the nuclei frequently had a wavy outline. Lysosomes were pushed away by the mitochondria. These cells appeared in clusters or in follicles (Fig. 1). However, some small follicles had maintained a nearly normal aspect with a larger than normal number of rounded rough endoplasmic cisternae (Fig. 2). Many follicular cells appeared intermediary between normal and mitochondria-rich cells. In some parts of their cytoplasm, swollen mitochondria were accumulated whereas in the other parts, the organelles appeared normally distributed.

Cells characterized by large areas of homogeneous cytoplasmic matrix with rare dilated cytoplasmic sacs were sporadically encountered.

Some follicles were made up of multilayered "fibrillar cells" having a high concentration of fibrils (20 nm wide), largely dispersed in the cytoplasm contrasting with the scarcity of the other organelles (Figs. 3 and 4). Many interfoldings existed between these cells the nuclei of which were frequently irregular in shape and in the cytoplasm of which rare dilated rough endoplasmic cisternae and some swollen mitochondria persisted between a filamentous meshwork. The microvilli were short and rare at the apex of the cells bordering the colloid lumen. The colloid of these follicles appeared more heterogeneous and denser than normally: the lumen contained dark cellular debris with fibrillar transformation, and a clear heterogeneous coating very often separated the apex of the bordering cells from the dense colloid (Fig. 4). Some cells with one or two cilia at the apex were found with clusters of fibrils distributed throughout a filamentous cytoplasm containing

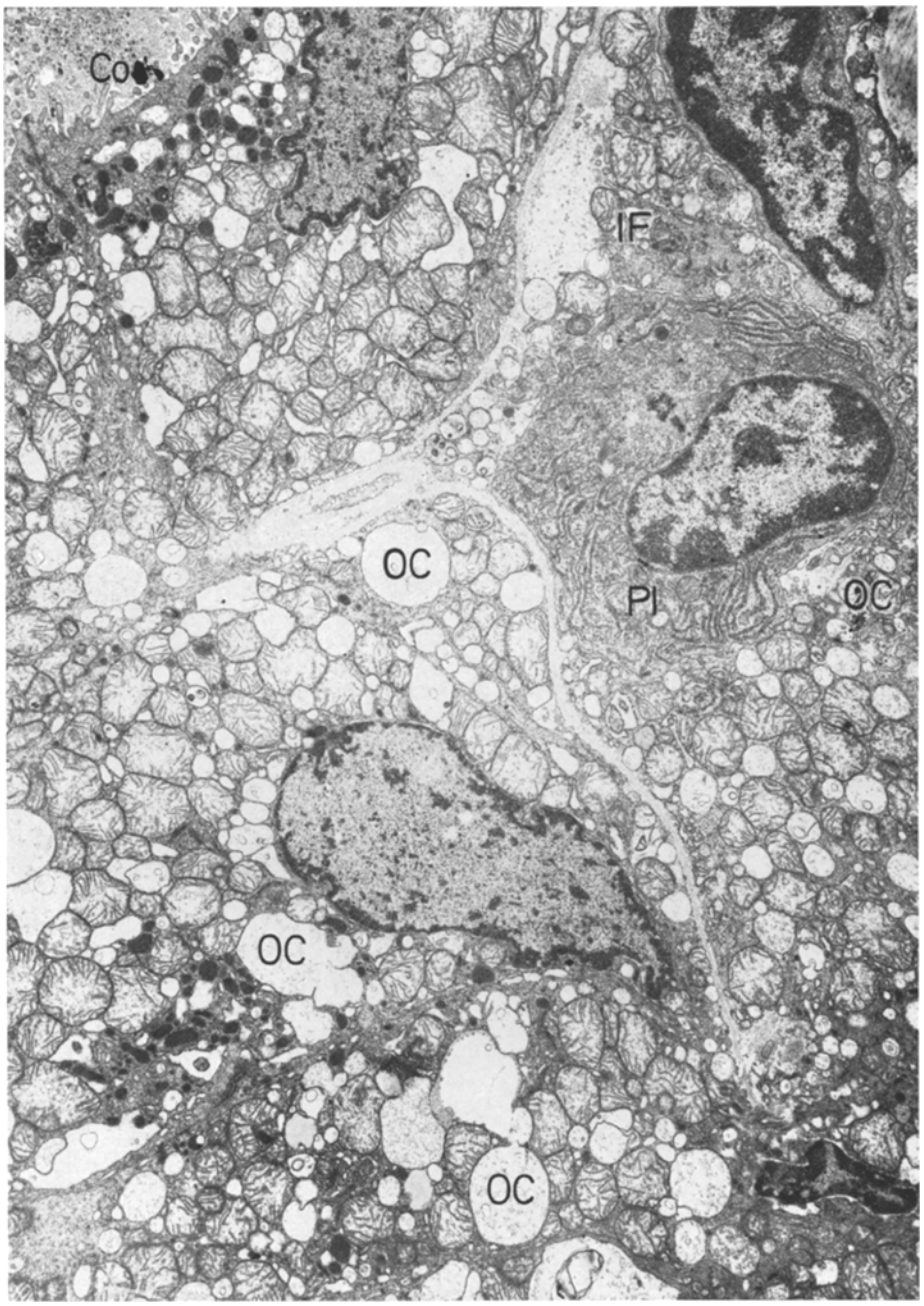

Fig. 1. Cluster of oncocytes (*OC*). In the upper-left corner, a part of a colloid lumen (*Co*) bordered by follicular cells transforming into oncocytes. A plasmocyte (*Pl*) and other inflammatory cells (*IF*) are visible. × 6500

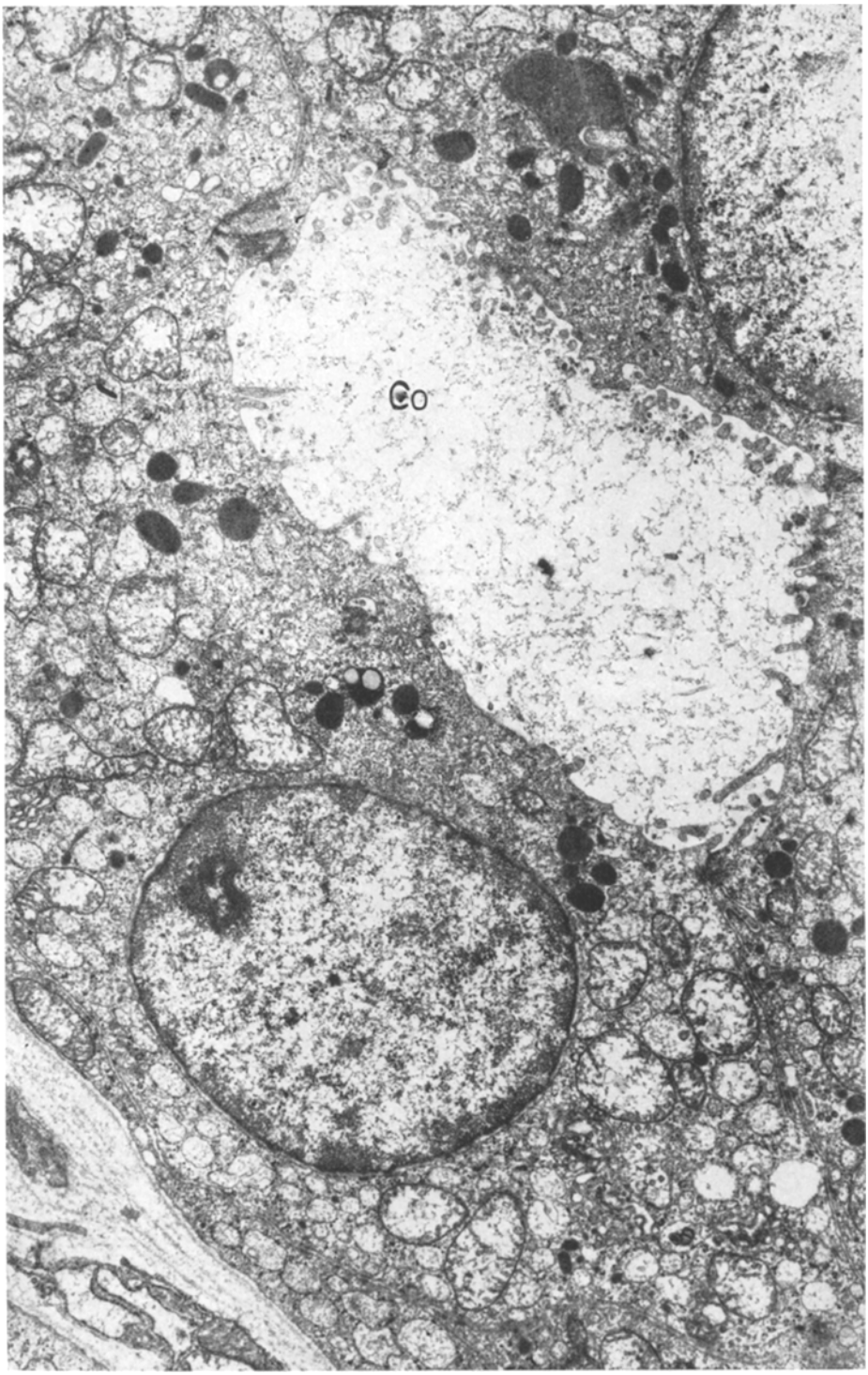

Fig. 2. Part of a follicle with colloid lumen (*Co*) bordered by nearly normal thyroid cells with rounded rough endoplasmic cisternae and swollen mitochondria. No pseudopods and no colloid droplets are seen: only lysosomes are present. × 12500

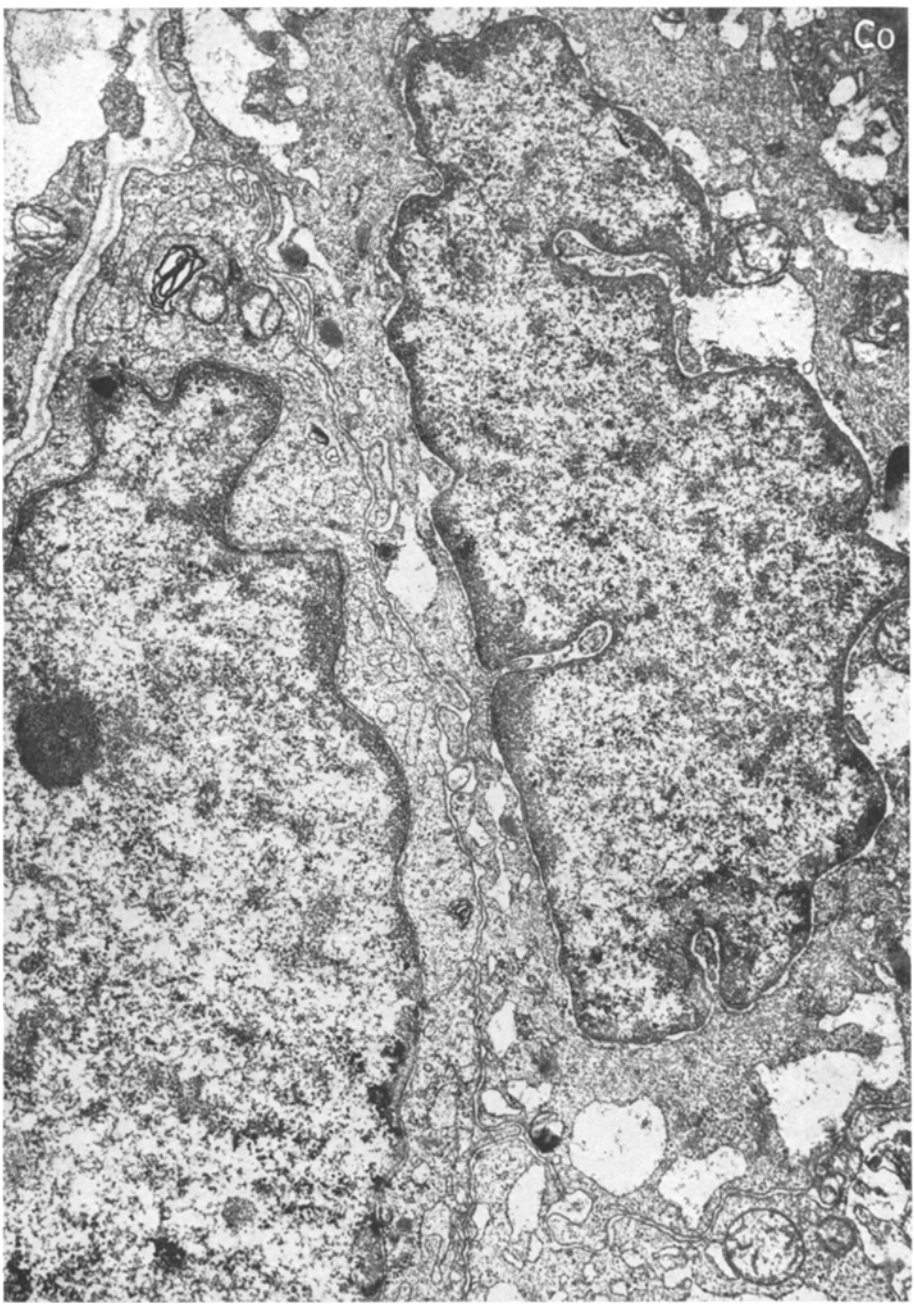

Fig. 3. Multilayered "fibrillar cells" bordering a colloid lumen a part of which is visible in the upper-right corner (*Co*). Fibrils are dispersed throughout the cytoplasms, whereas the other organelles are rare. × 12500

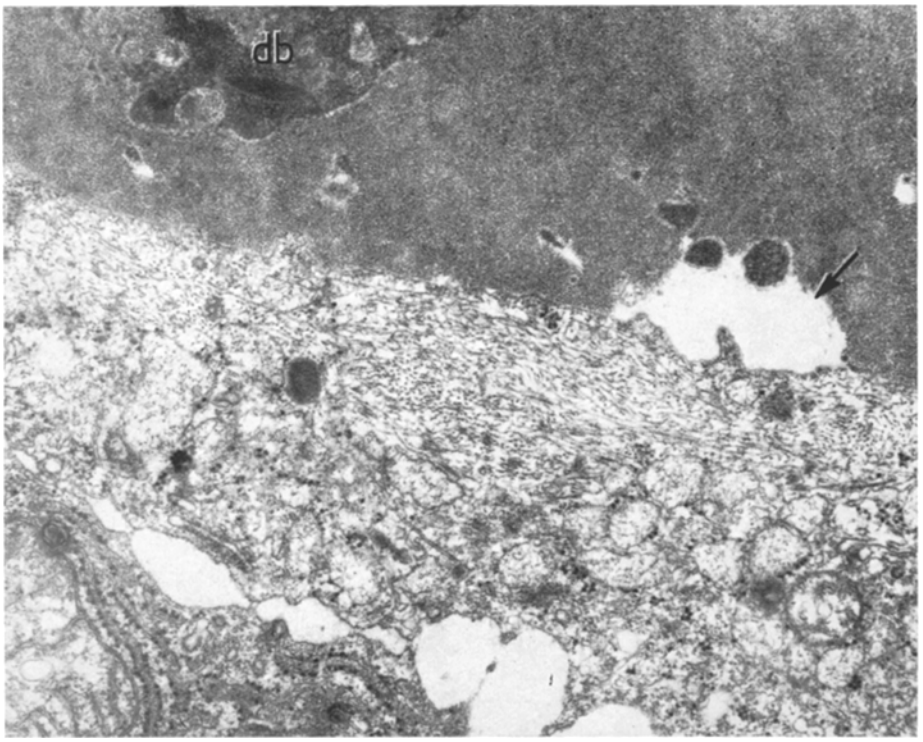

Fig. 4. Part of a "fibrillar cell" bordering the lumen of a particular follicle, the colloid of which appears dense and heterogeneous: cell debris (*db*) are present and, at the apex of the cell, exists a coating (arrow) separating the short microvilli from the dense colloid. × 14000

free polyribosomes and coated vesicles. Some coating also existed at the apex of these cells (Fig. 5).

Fibrillar cells were found associated in follicles or mixed with mitochondria-rich-cells and usual follicular type cells. Some mitochondria-rich-cells displayed fibrillar areas separating accumulations of mitochondria (Fig. 6). In no cell type, pseudopods and colloid droplets were observed. No parafollicular cell was encountered.

2. Inflammatory Cells

Numerous inflammatory cells were present in the connective tissue surrounding the parenchyma remnants. These cells were principally lymphocytes and plasmocytes; however, a few monocytes and macrophages invaded the basement membrane between the follicular cells.

Discussion

Most of the thyroid gland in adult hypothyroidism is principally made up of connective tissue. Nevertheless, after numerous serial semithin sections, it is possible to encounter areas occupied by inflammatory cells and thyroid follicle

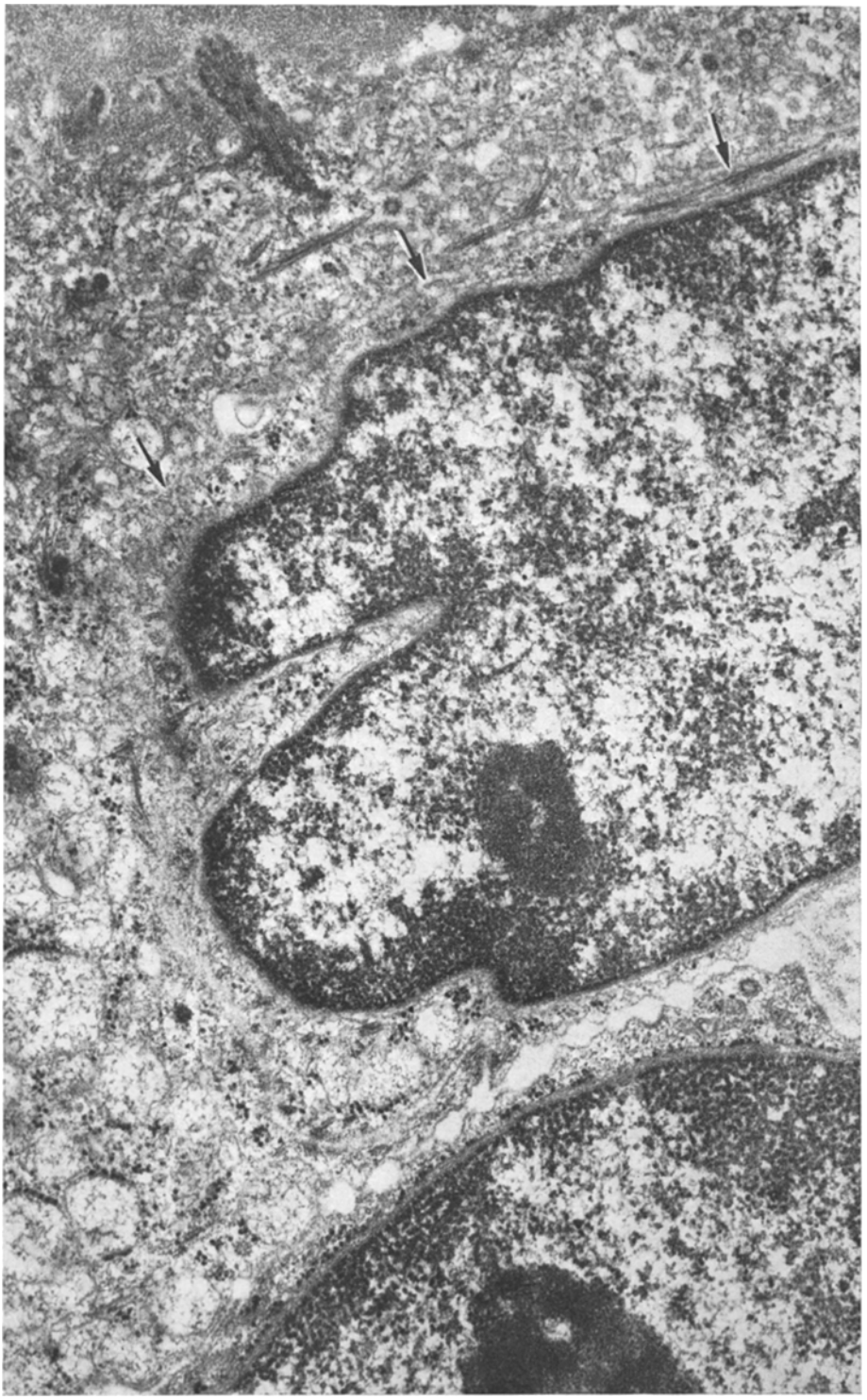

Fig. 5. Two-layered "fibrillar cells" continuing with a one-layered usual follicular cell and bordering a colloid lumen. The limits between the fibrillar cells are underlined by arrows. The apex of the upper fibrillar cell shows a cilium and a coating. × 26000

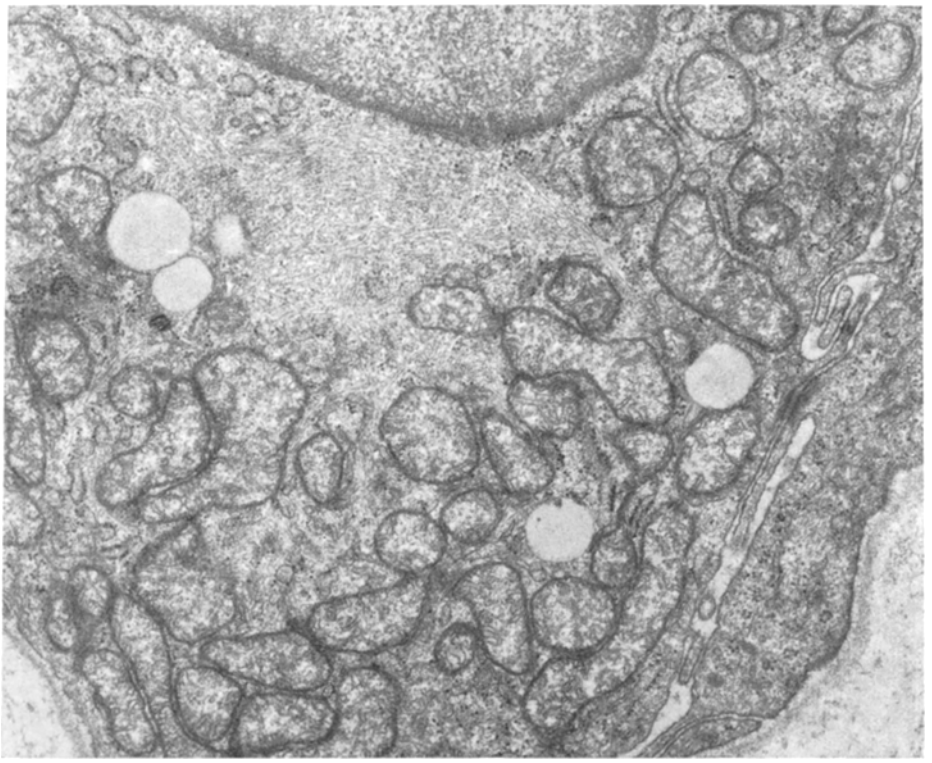

Fig. 6. An oncocyte in the cytoplasm of which an accumulation of fibrils seems to push away the mitochondria. × 18500

remnants. In such areas, the electron microscope reveals an ultrastructural aspect quite similar to that described in different varieties of chronic autoimmune thyroiditis (Irvine and Muir, 1963; Nève, 1966 and 1969; Brandes, Anton, and Orbegoso, 1969; Harris, 1969; Reidbord and Fisher, 1973). Mitochondria-rich-cells correspond to oncocytes which represent the prominent parenchymatous cells. These oncocytes are transformed thyroid cells as suggested by the existence of transitional cellular forms: cells in some parts of their cytoplasm look like normal thyroid cells, whereas some other cytoplasmic areas contain accumulations of swollen mitochondria. Undoubtedly, oncocytes in thyroid inflammation represent the specific cell type of autoimmune thyroiditis (see literature in Bastenie and Ermans, 1972). They are not observed in De Quervain's subacute thyroiditis (Nève, 1970). Nothing is known as to whether these oncocytes are the primum movens or the consequence of the disease. Because of their lack of ergastoplasmic machinery, they do not produce any hormone as suggested by biochemical studies (Hamperl, 1950; Tremblay and Pearse, 1960; Harcourt-Webster and Stott, 1966; Hübner, Paulissen and Kleinsasser, 1967).

Some rare follicles have maintained the characteristic aspect of the normal human follicular cell (Nève, 1965; Heimann, 1966; Klinck, Oertel and Winship,

1970), although some rough endoplasmic cisternae are fairly dilated and the number of free polyribosomes seems to be increased. However, no colloid droplets and no apical pseudopods are present. This feature is somewhat puzzling as blood thyrotropin levels being elevated, it should be normal to recognize morphological aspects of colloid phagocytosis and hormonal secretion (Wetzel and Wollman, 1969; Stein and Gross, 1964; Seljelid, 1967). Perhaps in these conditions of chronic thyrotropin stimulation, the thyroid secretion process occurs in a different way without colloid phagocytosis (Nève and Dumont, 1970; Ketelbant-Balasse, Rodesch, Nève and Pasteels, 1973).

Like in any autoimmune thyroiditis, a third cell type was exceptionally encountered. This type with large areas of hyaloplasmic matrix corresponds to the "colloid cells" the ultrastructure and signification of which have been described in a previous paper (Nève, Eagleton and Wollman, 1970).

A completely new and fourth cell type characterizes the ultrastructural aspect of the thyroid in adult hypothyroidism. It corresponds to the grey-coloured cells observed with light microscope and arranged in pluristratified follicles or in cords. These cells have a high concentration of fibrils largely dispersed in the cytoplasm contrasting with the scarcity of the other organelles. The origin of these "fibrillar cells" remains unknown. These cells might represent the final progeny of oncocytes: indeed some seem to accumulate microfilamentous material. Another interpretation remains that they might have an ultimobranchial origin (Vandyke, 1944, 1945, 1959). Indeed, these cells resemble the "U cells" described in the so-called ultimobranchial follicles of the thyroid gland in the rat (Nève and Wollman, 1971; Wollman and Nève, 1971; Calvert, 1972). Several features are common between these "fibrillar cells" in the man and the "U cells" in the rat: little granular reticulum, abundance of fibrils, shortness of the microvilli, interfoldings between cells, multilayering of cells surrounding the colloid lumen containing cell debris and an amorphous material coating the apical cellular surfaces. Moreover, ciliated cells with cytoplasmic fibrillar material observed in the present study recall the existence of ciliated cells in the unusual thyroid follicles in the mouse. These follicles are also considered as having an ultimobranchial origin (Wetzel and Wollman, 1969).

Ultimobranchial follicles in the human thyroid have already been described in light microscopy (Sugiyama, 1967) but necessitate many meticulous serial sections in order to be demonstrated. In hypothyroidism, as most of the typical follicles have vanished and as the ultimobranchial follicles probably have been maintained, the latter would become easier to identify. Nevertheless, the assimilation of the "fibrillar cells" in hypothyroidism to ultimobranchial cells could be questioned because of the lack of parafollicular cells usually associated with the ultimobranchial cells. Although less abundant in the human being (Braunstein and Stephens, 1968; Teitelbaum, Shieber and Moore, 1970) than in other species, the absence of parafollicular cells in the present material is puzzling: unfortunately, no calcitonin-assay was performed.

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