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The Cytology of the Adenomatous, Atrophic, and Hyperplastic Parathyroid Glands of Man

A Light- and Electron-Microscopic Study*

By

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With 20 Figures in the Text

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The secretory product of the parathyroid gland has recently been shown by RASMUSSEN and CRAIG to be an unbranched polypeptide. The nature of the secretory mechanism has not been clearly established, however.

WEYMOUTH and WEYMOUTH and BAKER demonstrated argyrophilic granules in the parathyroid glands of several species and demonstrated changes in the number and distribution of these granules in various secretory states. Hematoxylin-positive granules were demonstrated in the parathyroid glands of the Virginia deer, the barasingha deer, and the sheep by GRAFFLIN (1). These granules did not change with season, the sex of the animal, pregnancy, or lactation [GRAFFLIN (2)]. DE ROBERTIS, BENSLEY, and ROSOF demonstrated by light microscopy vacuoles and bodies that they felt represented the secretory products of the parathyroid glands. LEVER (1 and 2), studying the ultrastructure of the parathyroid glands of the rat, and TRIER, using the glands of the monkey *(Macaca mulatta)*, did not definitely identify the secretory granules. DAVIS and ENDERS described secretory granules in the parathyroid glands of the rat but felt that they coalesced into multivesicular bodies. LANGE, studying human parathyroid adenomas, identified electron-dense bodies in several of the cell types but did not establish them as the secretory granules. MUNGER and ROTH, studying the normal parathyroid glands of the Virginia deer and the human, in a combined light- and electron-microscopic study, found rod-shaped, sometimes membrane-limited electron-dense granules that they identified as the secretory granules. These granules were the same as the argyrophilic granules of WEYMOUTH and BAKER and the hematoxylin-positive granules of GRAFFLIN (1). MUNGER and ROTH felt that similar granules were present in the electron micrographs of LEVER (1, 2) and TRIER and that the granules were the same as those seen by LANGE and by DAVIS and ENDERS, though they did not coalesce into multivesicular bodies.

In order to delineate more clearly the mechanism of parathyroid hormone secretion and control and to prove the nature of the secretory granules and their relation to the secretory process, a study of the parathyroid glands from four patients with primary hyperparathyroidism was undertaken.

Two of the patients had parathyroid adenomas, and two patients had primary chief cell hyperplasia. The patients with adenomas afforded the unique opportunity to study the human parathyroid gland in a state of depressed parathyroid secretion (i.e., the rim of "normal" parathyroid gland about a hyperfunctioning parathyroid adenoma).

Material and Methods

Fresh parathyroid tissue was obtained in the operating room from four patients with primary hyperparathyroidism.

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Patient 1. A 44-year-old white male with renal stones and questionable roentgenographic changes of the bones had a serum calcium level ranging from 12.0 mg-% to 12.3 mg-% and a serum phosphorus level ranging from 2.3 mg-% to 2.8 mg-%. The tumor was reddish-tan, oval, and weighed an estimated 250 mg.

Patient 2. A 52-year-old white female with renal stones and minimal osseous changes had a serum calcium level that ranged from 11.1 mg-% to 13.2 mg-% and a serum phosphorus level ranging from 1.8 mg-% to 2.6 mg-%. The tumor was chocolate brown, weighed 1.2 g, and was composed of two apposed spheres of slightly different sizes.

Patient 3. A 43-year-old white female with severe osteoporosis, multiple neurofibromatosis, and renal stones whose serum calcium values ranged from 9.1 mg-% to 10.8 mg-% and whose serum phosphorus level ranged from 1.5 mg-% to 2.0 mg-%. The alkaline-phosphatase level ranged from 27 to 70 King Armstrong units. All four glands were enlarged to approximately twice normal size.

Patient 4. A 51-year-old white female with a history of multiple, functioning islet cell adenomas that had required resection of the pancreas for hyperinsulinism 10 years prior to parathyroidectomy. Following pancreatectomy she had a gastric ulcer and renal stones. The serum calcium level ranged from 2.0 mg-% to 3.0 mg-%, and the serum phosphorus from 10.0 mg-% to 12.0 mg-%. At operation all four parathyroid glands were enlarged; three measured 1.5 cm by 0.5 cm by 0.5 cm, and the fourth measured 0.7 cm by 0.5 cm by 0.3 cm.

Each specimen from these four patients was divided. Part of the tissue was placed in buffered neutral formalin and embedded in paraffin for light microscopy; the remaining tissue was cut into 0.5 to 1 mm spheres and placed in Dalton's buffered 2% osmium tetroxide and embedded in methacrylate and Epon 812 (LUFT) for light and electron microscopy. The paraffin sections were stained with hematoxylin and eosin, chrome alum hematoxylin, iron hematoxylin, periodic acid-Schiff (PAS), with and without diastase digestion, and BODIAN protargol silver stain. The methacrylate sections were stained with hematoxylin and phloxine (H & P) and with PAS, with and without diastase digestion [MUNGER (2)]. The Epon blocks were sectioned with Porter-Blum Servall microtomes equipped with glass knives. Unstained sections and sections stained with uranyl acetate and lead subacetate were examined with RCA EMU 3 D and F electron microscopes.

Light-Microscope Observations

Patient 1. The *hematoxylin* and *eosin* preparations of the tumor reveal sheets and cords of chief cells and vacuolated chief cells (Fig. 1 a), 8 to 12 μ in diameter. Rarely an oxyphil cell is seen. The cell membranes are well defined, and there is minimal variation in cell size. The nuclei show moderate variation in size; and hyperchromatic, giant single nuclei are frequently present. The tumor capsule is thin and composed of loose fibrous tissue. A few fat cells are present in the capsule, but none in the tumor. Outside of the capsule a rim of parathyroid tissue (Fig. 1 b) shows sheets of small chief cells, 7 to 9 μ in diameter. Most of these have a slightly eosinophilic cytoplasm, but a few are vacuolated. There is an abundant fibrous stroma, with numerous fat cells in this stroma. This is interpreted as a rim of "normal" parathyroid, confirming the diagnosis of an adenoma (ROTH).

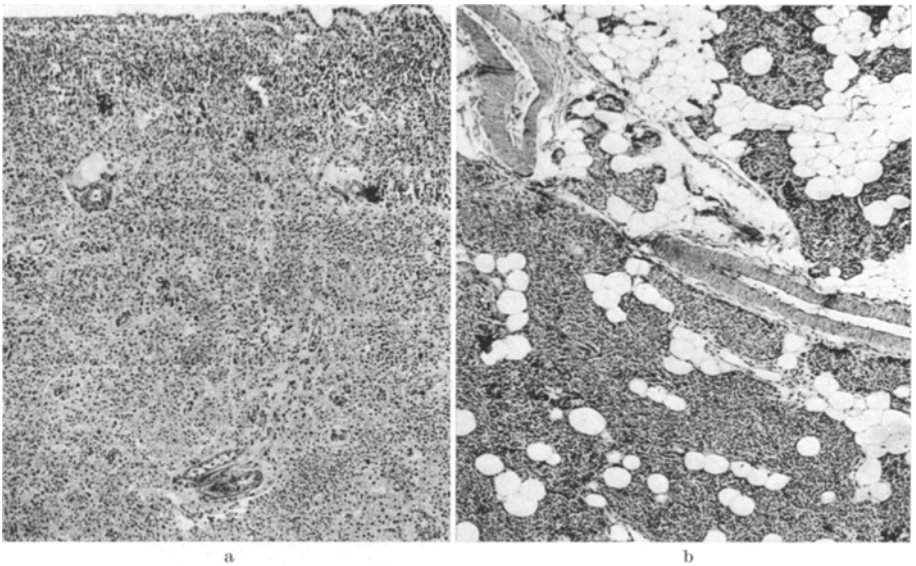
Bodian stain reveals numerous argyrophilic granules in the cytoplasm of the tumor cells (Fig. 2). The cytoplasm also contains smaller, much less distinct granules that stain blue with chrome alum hematoxylin and iron hematoxylin. The distribution of these granules is similar to that of the argyrophilic granules. The hematoxylin staining of the granules is less distinct than the silver staining, and the granules appear larger with the silver stains, probably because of deposition of silver on the granules. These granules appear identical to those found by MUNGER and ROTH in normal human parathyroids. The tumor cells contained abundant PAS-positive, diastase-digestible material, presumably glycogen.

The chief and oxyphil cells of the rim of parathyroid tissue outside of the tumor capsule contain only a very rare Bodian-positive granule (Fig. 3), and it is not possible definitely to identify hematoxylin-positive granules. There is a large amount of glycogen in these cells.

Patient 2. The *hematoxylin* and *eosin* preparations show sheets, cords, and acini of oxyphil cells 10 to 12 μ in diameter (Fig. 4). In a few areas there are groups of smaller chief cells and some vacuolated chief cells. A few fat cells are present in and near the thin, fibrous

capsule. Outside of the capsule are sheets of small chief cells, with less cytoplasm than in the normal chief cell. These are embedded in an abundant fibrous stroma containing a large number of fat cells. This again is interpreted as a rim of "normal" parathyroid tissue, which confirms the diagnosis of parathyroid adenoma (ROTH).

The *Bodian stain* shows large numbers of argyrophilic granules in the tumor, mostly in the chief cells. The oxyphils contain occasional granules. The chrome alum hematoxylin and iron hematoxylin stains reveal a similar distribution of granules, slightly smaller and less distinct than those seen with the Bodian stain. Large amounts of glycogen are present in both types of cells (Fig. 5).



a b

Fig. 1. a Parathyroid adenoma from Patient 1 showing solidly packed chief cells with moderate variation in nuclear size. Hematoxylin and eosin. Mag. 55 ×. b Rim of normal parathyroid tissue around the adenoma (Fig. 1a) in Patient 1 showing sheets and cords of chief cells in a fatty stroma. Hematoxylin and eosin. Mag. 55 ×

The cells in the rim of parathyroid tissue outside of the tumor contain only rare argyrophilic granules, which cannot be identified with the hematoxylin stains. There is a large amount of glycogen in the cells.

Patient 3. All four glands were histologically identical, being composed of cords, sheets, and acini of oxyphil cells (Fig. 6). Only rare chief cells and a few fat cells are present. There is no rim of stroma containing normal parathyroid tissue around the glands. The histologic pattern is the same as that in two of the cases of *primary chief cell hyperplasia* described by COPE et al.

There are numerous large argyrophilic granules throughout the glands (Fig. 7). These granules are much more frequent and larger than those found in the normal human parathyroid, and larger than those in the adenomas, being more nearly the size of the granules seen in the Virginia deer (MUNGER and ROTH). The hematoxylin stains (Fig. 8) reveal many small granules, but they are smaller and less distinct than the argyrophilic granules. Large amounts of glycogen are present throughout the glands.

Patient 4. All four glands are composed of cords, sheets, and acini of chief cells. In some areas the stroma is very prominent, appearing edematous and causing wide separation of the epithelial cells. No rim of normal parathyroid tissue is seen around any of the glands, and this confirms the diagnosis of primary chief cell hyperplasia.

Large numbers of argyrophilic granules are present in most of the chief cells throughout the glands. These are similar in size, number, and distribution to those in the glands of Patient 3.

Electron-Microscope Observations

Adenomas

Patient 1. The predominating chief cells (Fig. 9) are polygonal and stellate, with mostly straight parallel membranes connected to each other by desmosomes.

Fig. 2

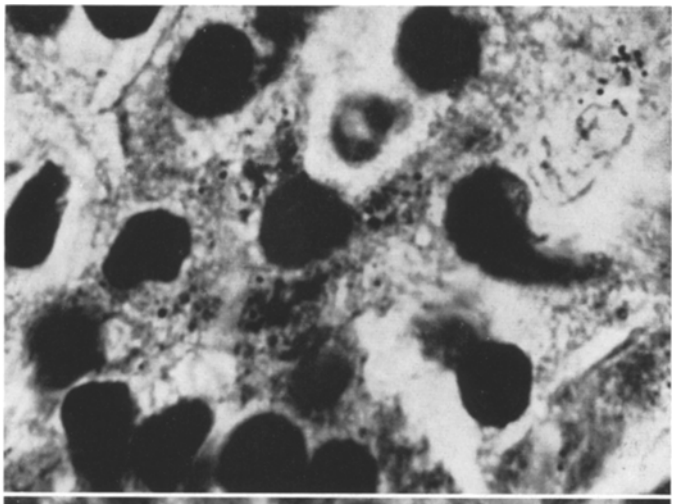


Fig. 3

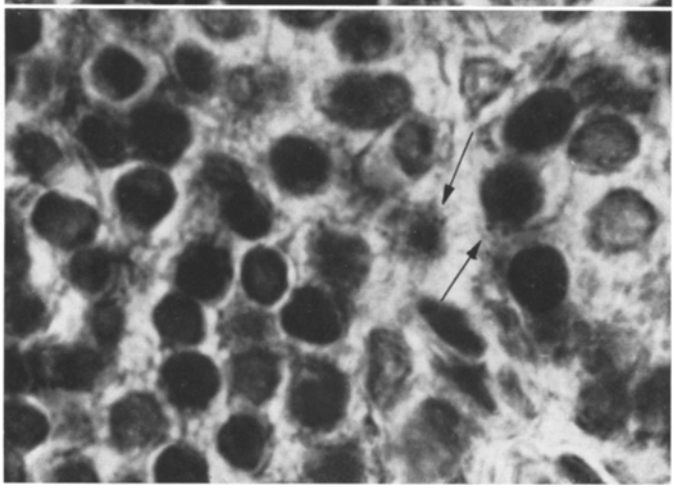


Fig. 2. Parathyroid adenoma from Patient 1 showing numerous argyrophilic granules in the cytoplasm of the chief cells. Bodian. Mag. 2700 ×

Fig. 3. Rim of normal parathyroid tissue about the adenoma in Patient 1 showing a few argyrophilic granules (arrows). Bodian. Mag. 2240 ×

However, in some zones there is marked interdigitation of cell membranes, and in areas the intercellular spaces are greatly expanded and lined by folds of cell membranes. The cytoplasm of the chief cell is finely granular and often contains large amounts of glycogen. Lipid bodies, from 100 mμ to 5 μ, often multilocular, and sometimes indenting the nucleus, are seen.

In groups and individually, many of the chief cells contain round to rod-shaped, electron-dense granules (Fig. 9). They range from 10 mμ to 100 by 300 mμ. The granules occasionally branch, are occasionally bent, and sometimes have a demon-

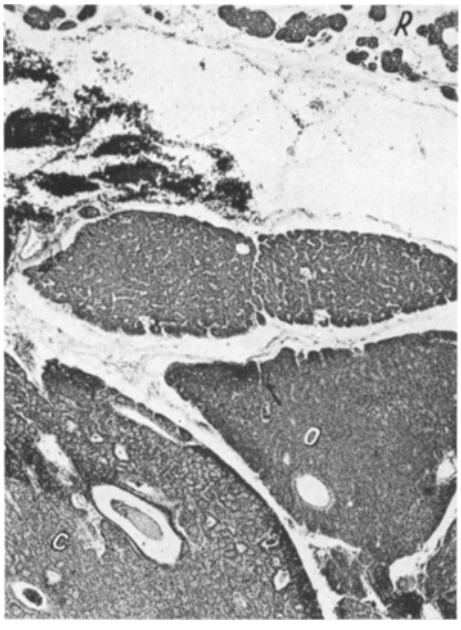
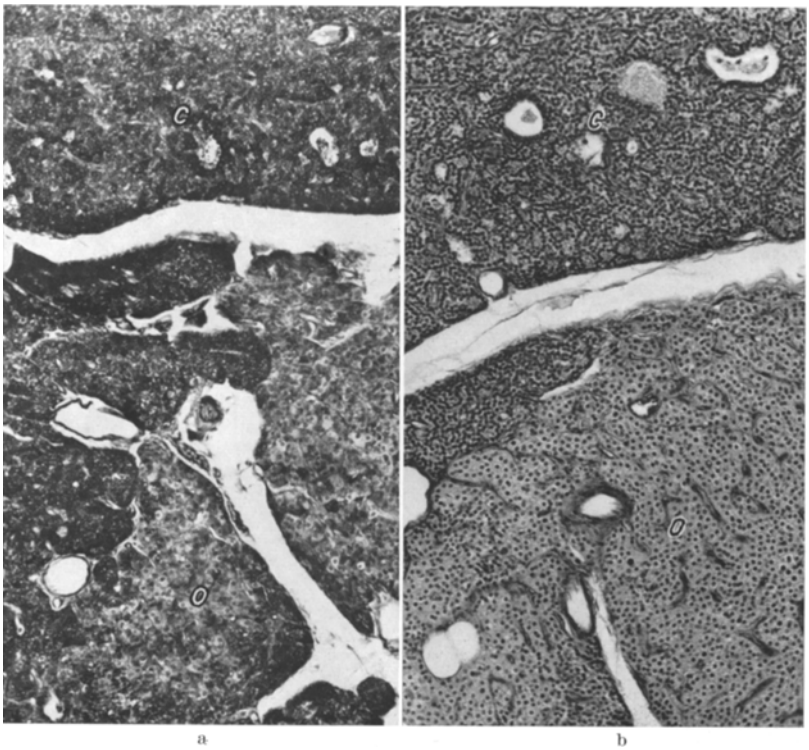


Fig. 4. Parathyroid adenoma from Patient 2 showing sheets, cords, and acini of chief cells (*c*) and oxyphil cells (*o*). A rim of normal parathyroid (*R*) shows cords of chief cells in a fat-filled stroma. Hematoxylin and eosin. Mag. 50 ×



a b

Fig. 5. a Parathyroid adenoma from Patient 2 showing cytoplasm of chief cells (*c*) and oxyphil cells (*o*) filled with periodic acid-Schiff-positive granules. Periodic acid-Schiff. Mag. 115 ×. b Parallel section showing disappearance of granules after diastase digestion. Chief cells (*c*), oxyphil cells (*o*). Periodic acid-Schiff. Mag. 115 ×

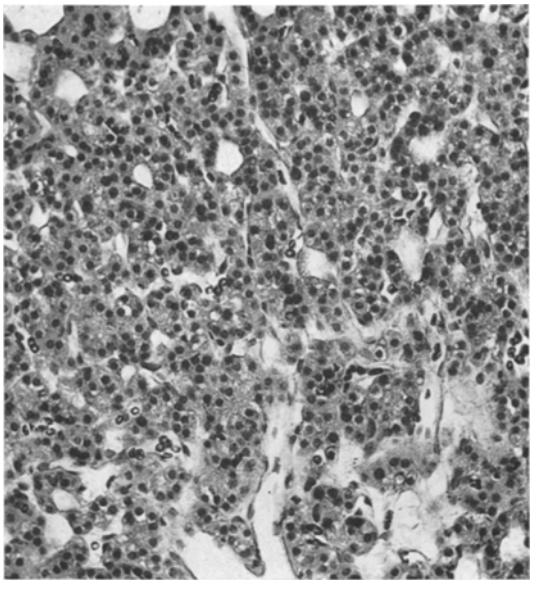


Fig. 6. Primary chief cell hyperplasia from Patient 3 showing cords, sheets, and acini of oxyphil cells. Hematoxylin and eosin. Mag. 200 ×

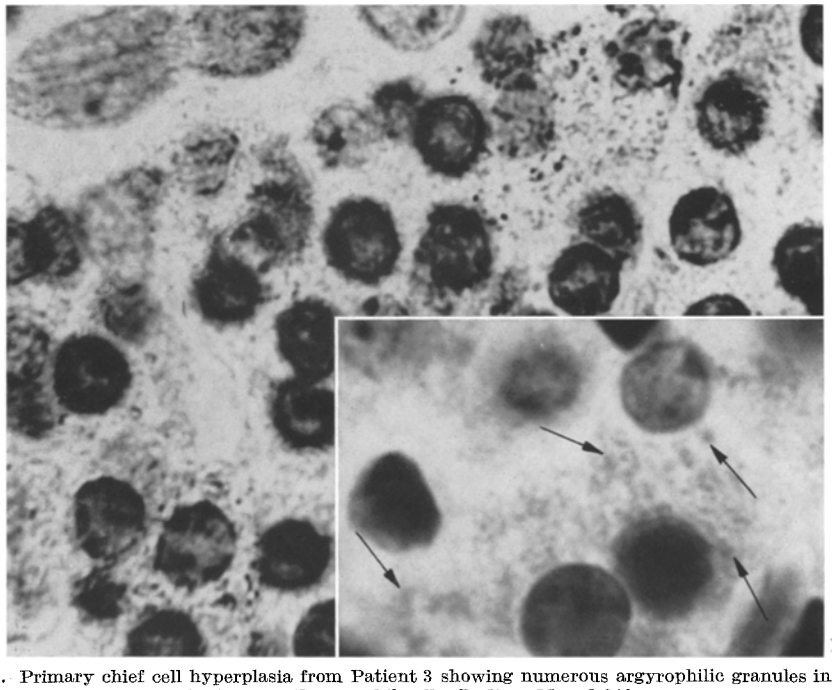


Fig. 7 Fig. 8

Fig. 7. Primary chief cell hyperplasia from Patient 3 showing numerous argyrophilic granules in the cytoplasm of the oxyphil cells. Bodian. Mag. 2,240 ×

Fig. 8. Primary chief cell hyperplasia from Patient 3 showing numerous hematoxylin-positive bodies (arrows) in the cytoplasm of the oxyphil cells. Heidenhain iron hematoxylin. Mag. 2700 ×

strable limiting membrane. The larger granules have a granular fine structure. Some contain extremely electron-dense round bodies 1 to 2 mμ in diameter. In

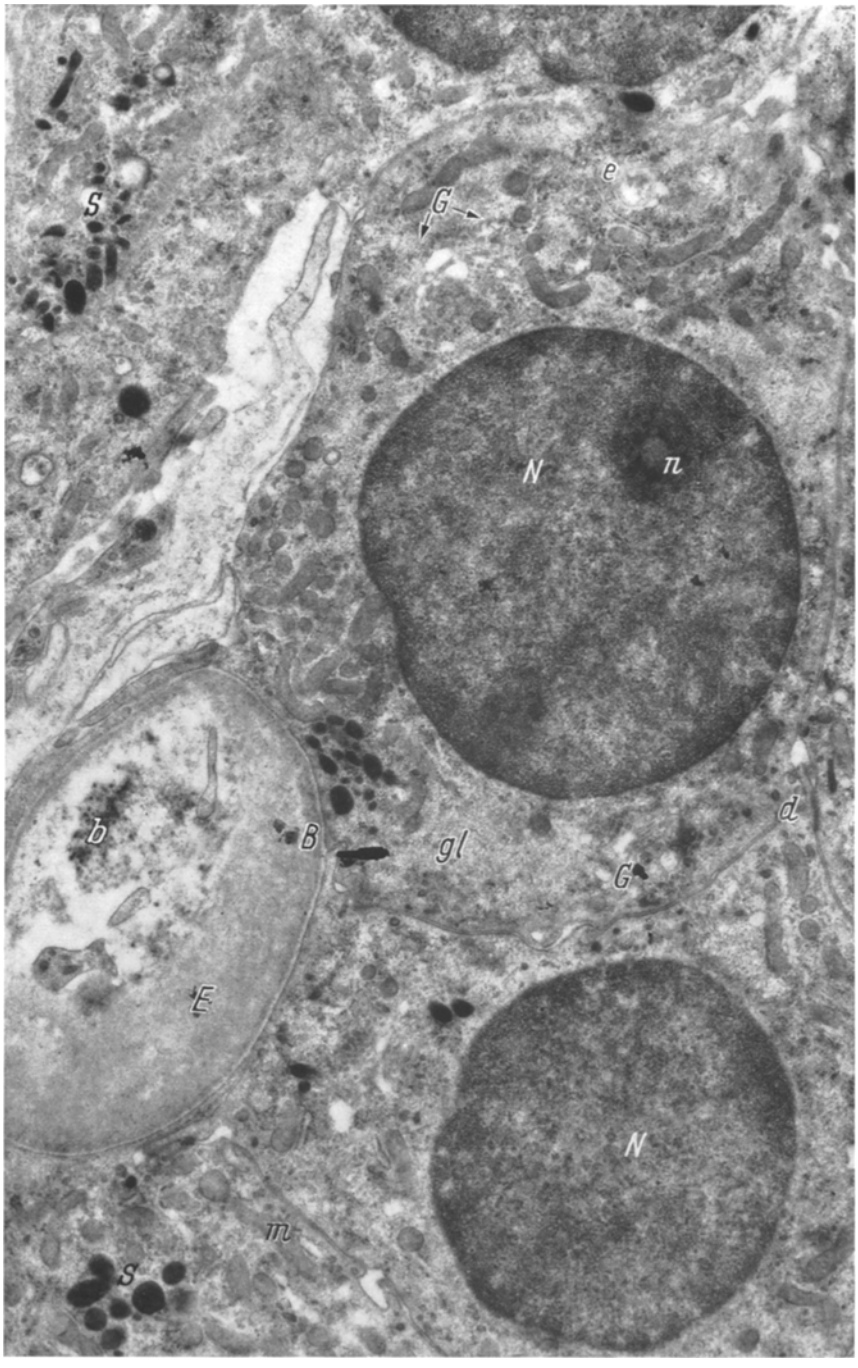


Fig. 9. Electron micrograph of a group of actively secreting chief cells from the parathyroid adenoma from Patient 1. All of the cells seen contain secretory granules (*S*). The Golgi apparatuses (*G*) are prominent and contain small secretory granules and vacuoles. Many of the cells contain large amounts of glycogen (*gl*). Nuclei (*N*), nucleolus (*n*), ergastoplasm (*e*), mitochondria (*m*), desmosomes (*d*), basement membrane (*B*), extracellular space (*E*), collagen fibers (*b*). Uranyl acetate. Mag. 11,500 ×

the region of the Golgi apparatus are numerous small granules, probably prosecretory granules, and small vacuoles varying in electron density from the density of the vacuoles within the Golgi membranes to that of the larger granules. The number and distribution of the larger granules corresponds to that of the argyrophilic granules. The Golgi apparatuses are large and composed of lamellar sacs, vesicles, and tubes of smooth membranes (Fig. 10). Often the Golgi apparatus is arranged in a perinuclear cap. In contrast to the normal parathyroids, no

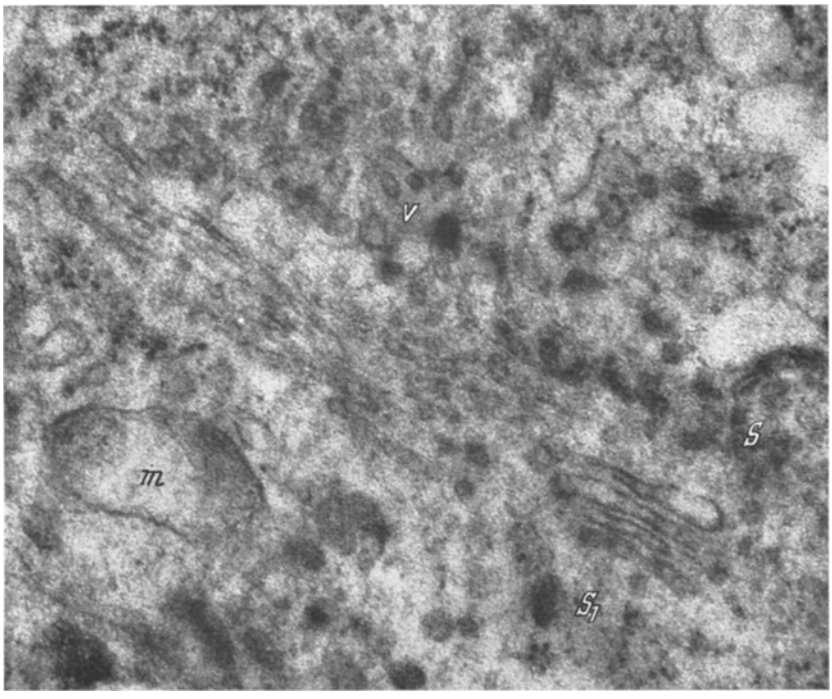


Fig. 10. Electron micrograph of the region of the Golgi apparatus from an actively secreting chief cell in the adenoma from Patient 1. The parallel arrays of smooth-walled membranes are surrounded by secretory vacuoles (V) of various electron densities and by small prosecretory granules (S). The large secretory granule (S_1) has a granular fine structure and small areas of increased density. Vacuolated mitochondria (m). Uranyl acetate. Mag. 61,500 ×

relationship between the amount of glycogen and the number of secretory granules is present in the adenoma.

The ergastoplasm of the chief cells is composed of both membranes with ribonucleoprotein granules and free ribonucleoprotein particles. In some cells parallel rows of ergastoplasmic sacs are prominent, and these may correspond to the juxtanuclear bodies of PAPPENHEIMER and WILENS. The mitochondria are variable in number, ranging from 5 to 50 per cell, are rod-shaped, often bent, and measure 100 to 300 mμ in diameter and 300 to 1,800 mμ in length. They have the usual bilaminar outer membrane with the cristae tightly packed and arranged in parallel interdigitating sheets.

The chief cell nucleus is roughly round to oval, with irregular indentations. The nucleoplasm is homogeneous and granular and rarely has a nucleolus.

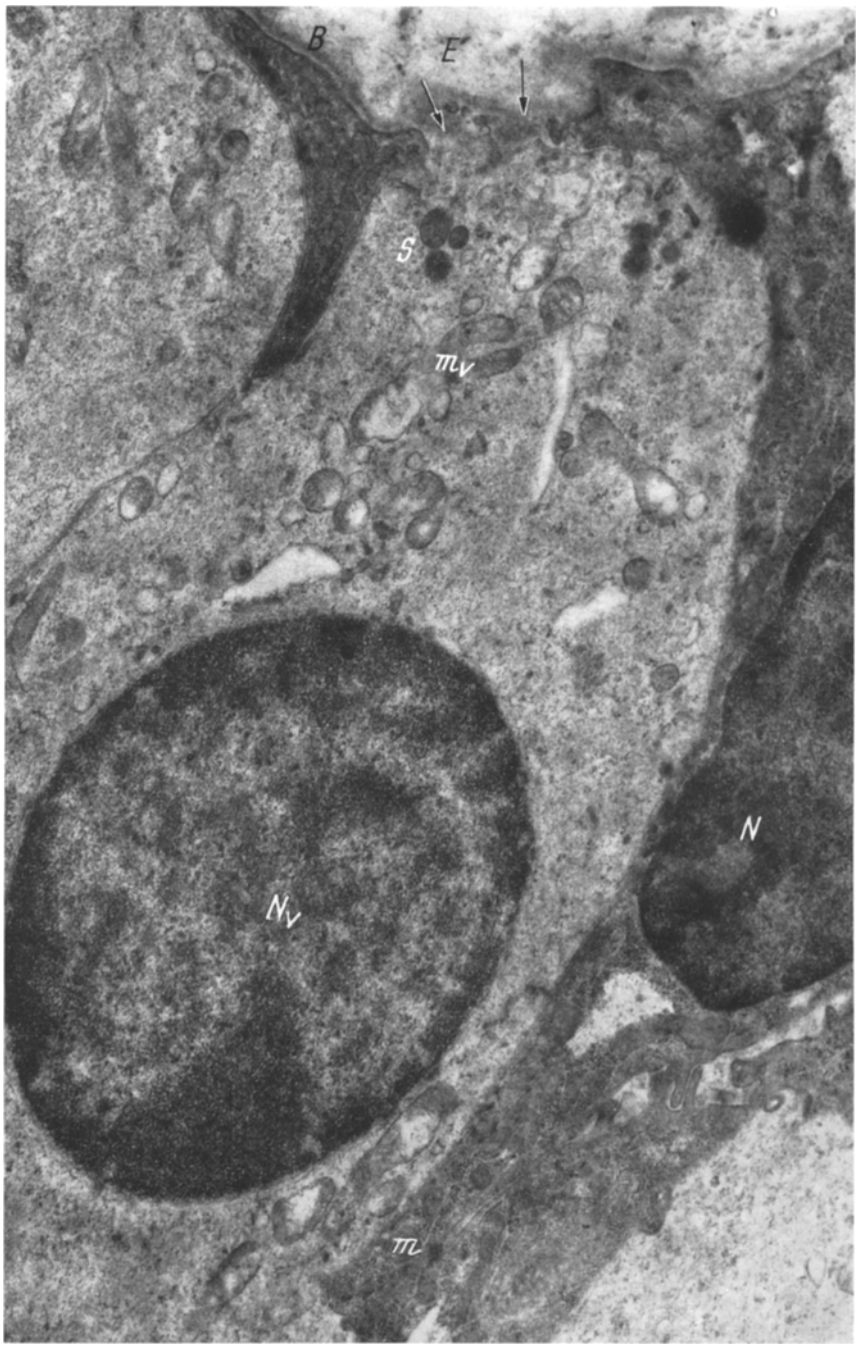


Fig. 11. Electron micrograph of two cells (vacuolated chief cells) with relatively electron-transparent cytoplasm from the adenoma from Patient 1. The mitochondria ($m\bar{v}$) are somewhat swollen and vacuolated, and the cell membrane (arrows) does not appear completely intact. There are secretory granules (S) present, though no ergastoplasm or Golgi apparatuses can be identified. The cytoplasm of an adjacent oxyphil cell is filled with mitochondria (m). Nucleus of vacuolated cell ($N\bar{v}$), nucleus of oxyphil cell (N), basement membrane (B), extracellular space (E). Uranyl acetate. Mag. 34,000 ×

Scattered through the adenoma are cells slightly larger than the chief cell, and less often stellate (Fig. 11). The cell membranes are usually straight, and adjacent cells are occasionally connected by desmosomes. The cytoplasm is relatively electron-transparent and is granular. Electron-dense secretory granules are present, but usually only in small numbers. Golgi and ergastoplasm are not usually identifiable. The mitochondria, although usually vacuolated and not as numerous as in the chief cell, are identical to those of the chief cell in structure and size. These are felt to represent vacuolated chief cells or transitional water-clear cells (ROTH).

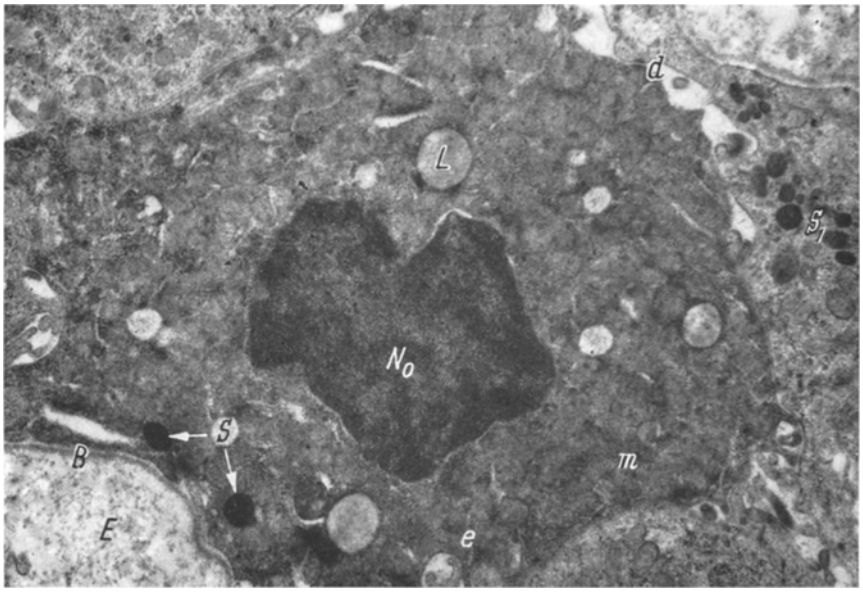


Fig. 12. Electron micrograph of an oxyphil cell surrounded by actively secreting chief cells in the adenoma from Patient 1. The oxyphil cell cytoplasm is filled with mitochondria (*m*), but contains secretory granules (*S*) and lipid bodies (*L*). It is connected to one of the adjacent chief cells by a desmosome (*d*). Nucleus of oxyphil cell (N_0), secretory granules of chief cell (S_1), extracellular space (*E*), and basement membrane (*B*). Uranyl acetate. Mag. 12,300 ×

Rarely an oxyphil cell (Fig. 12) is present. Such cells are identical in appearance to those from Patients 2 and 3 and will be described in full detail under Patient 2 in this section and under Patient 3 in the section on primary chief cell hyperplasia.

The perivascular spaces are very wide. A prominent basement membrane is present both adjacent to the parathyroid cells and surrounding the capillaries. At the basement membrane, adjacent parathyroid cells are usually in close approximation, though away from this membrane the intercellular spaces between adjacent cells may be expanded. In the perivascular spaces are unmyelinated nerve fibers, fibroblasts, and collagen bundles. In the capillary endothelial cells are often seen electron-dense, membrane-limited secretory granules (Fig. 13) of identical size, shape, and internal structure to those in the parathyroid epithelial cells.

Patient 2. The predominating cell is the oxyphil. This is polygonal, rarely stellate, with both straight and interdigitating cell membranes, and with desmo-

somes connecting adjacent cells. These cells are arranged in sheets, cords, and acini. Occasional groups of chief cells and vacuolated chief cells identical to those seen in Patient 1 are present. The chief cells contain most of the secretory granules (Fig. 14) and have large Golgi apparatuses and a prominent ergastoplasm. Most of

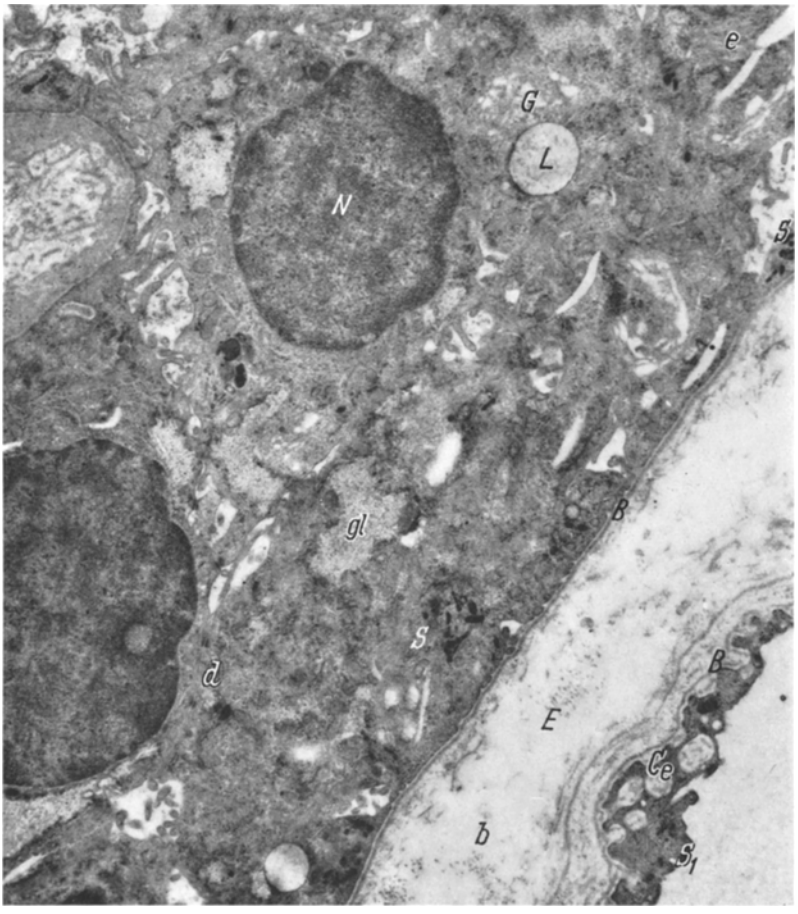


Fig. 13. Electron micrograph of an area of actively secreting chief cells from the adenoma from Patient 1. Note the presence of secretory granules (*S*), glycogen (*gl*), and Golgi apparatuses (*G*) in the chief cells. The cytoplasm of the capillary endothelial cell (*Ce*) contains numerous secretory granules (S_1). Extracellular perivascular space (*E*), basement membrane (*B*), desmosome (*d*), nucleus (*N*), collagen fibers (*b*), ergastoplasm (*e*). Uranyl acetate. Mag. 10,000 ×

the oxyphil cells are identical to the oxyphils of normal human parathyroids (Munger and Roth). The cytoplasm is largely filled with tightly packed, rod-shaped mitochondria with parallel lamellar cristae. The cytoplasm between the mitochondria is filled with granules of glycogen. Most of the oxyphil cells contain sparse ergastoplasm, a small Golgi apparatus, and only rare secretory granules. In some zones, however, the oxyphil cells contain prominent parallel sacs of granular ergastoplasm and a large Golgi apparatus (Fig. 15) composed of numerous parallel, smooth-walled sacs, vesicles, and vacuoles. In the Golgi region are seen numerous 10 to 20 mμ electron-dense prosecretory granules (Fig. 16), similar

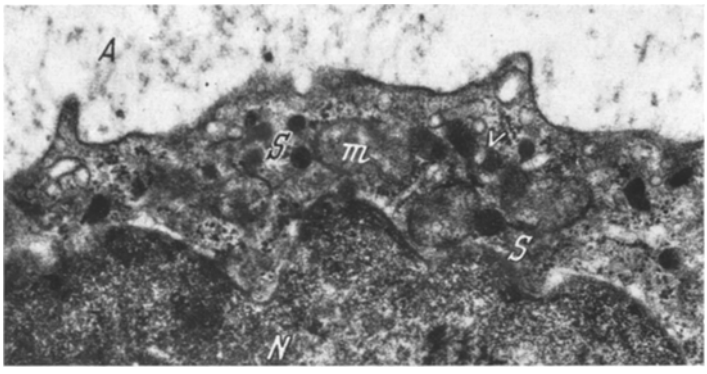


Fig. 14. Electron micrograph of a cell from the adenoma from Patient 2 containing several secretory granules (*S*), at the edge of a lumen (*A*) of an acinus. Nucleus (*N*), mitochondria (*m*), vacuoles (*v*), of unknown origin. Uranyl acetate. Mag. 21,500 ×

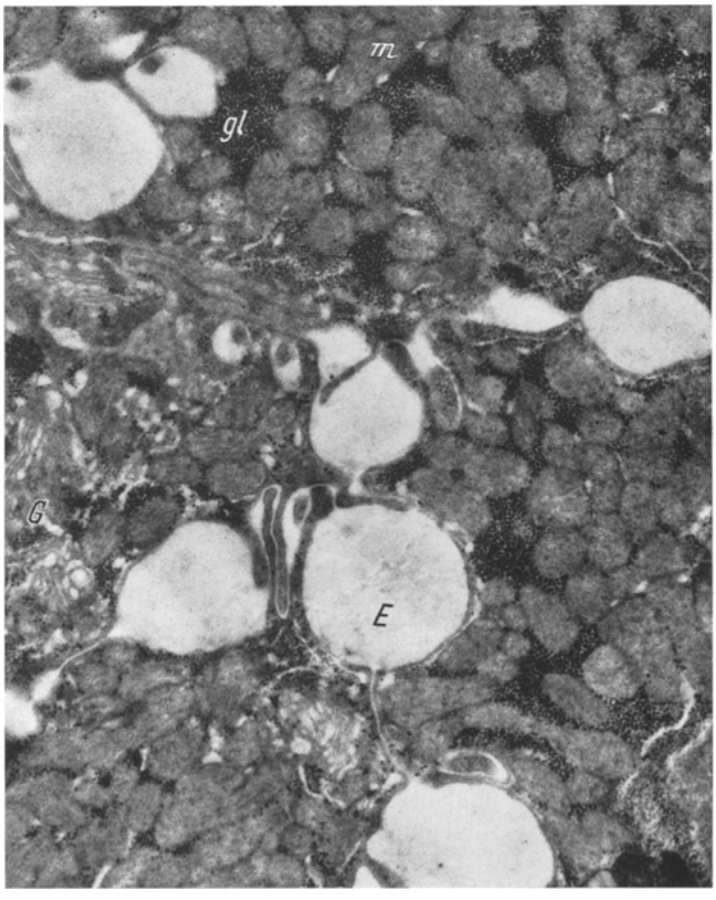


Fig. 15. Electron micrograph of two oxyphil cells from the adenoma of Patient 2 showing the cytoplasm filled with mitochondria (*m*) and glycogen (*gl*). The lower cell contains a prominent Golgi apparatus (*G*). Extracellular space (*E*). Lead subacetate. Mag. 22,000 ×

to those in the Golgi region of the cells from Patient 1. In groups and individually membrane-limited granular, round to rod-shaped secretory granules are seen in these cells. The nuclei are similar in appearance to those of the chief cell. Some acini are found, usually among the oxyphils. These acini are surrounded by cells whose surfaces are thrown up into folds resembling microvilli. Terminal bars connect adjacent cells at the edge of the acini. No basement membrane covers the luminal margin of the cells, but these acini are surrounded by basement

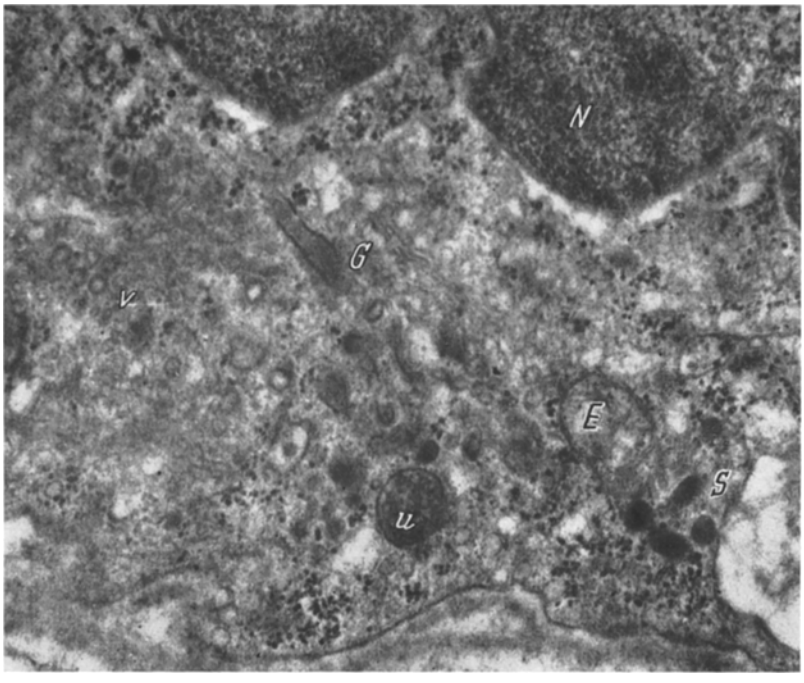


Fig. 16. Electron micrograph of a cell from the adenoma of Patient 2 with a prominent Golgi apparatus (*G*) and many prosecretory granules (*S*) of various sizes and densities. Nucleus (*N*), mitochondria (*m*), vacuoles (*v*), multivesicular body (*u*). Uranyl acetate. Mag. 28,800 ×

membranes. The extracellular spaces, as in Patient 1, are often expanded. The perivascular extracellular spaces are prominent, with basement membranes applied to the connective tissue of both the capillary endothelial and the parathyroid epithelial cell membranes. The perivascular spaces contain unmyelinated nerve fibers, fibroblasts, and collagen fibers.

Again in the capillary endothelial cells are sometimes found secretory granules identical to those seen in the parenchymal cells.

Atrophic Parathyroids

Patients 1 and 2. The predominant chief cells are polygonal and stellate (Fig 17). Only a rare oxyphil cell is seen. The usual arrangement of the cells is in nests and sheets, with rare acini. The nests of cells are interspersed between large amounts of fat-filled stroma. The cytoplasm of the chief cell, slightly less than in a normal

human chief cell and markedly less than in the adenomatous chief cell, is granular and moderately electron-dense. Only rare secretory granules are seen. There are

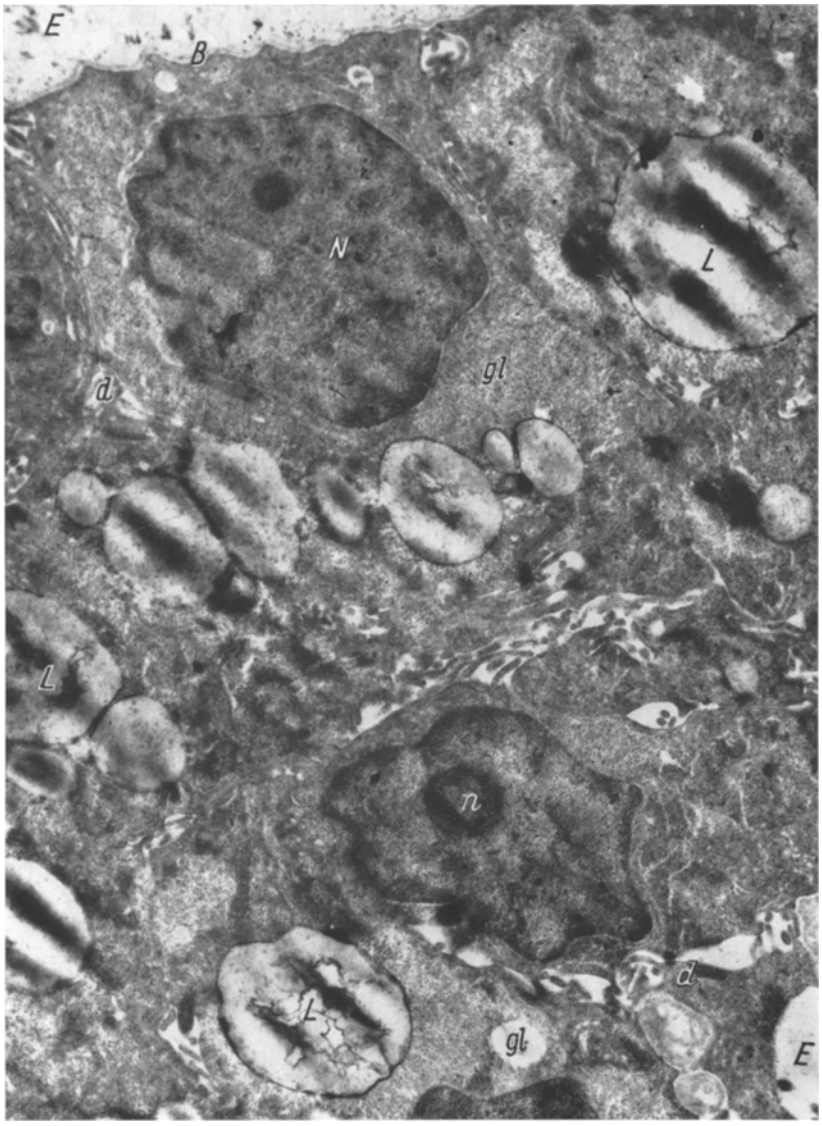


Fig. 17. Electron micrograph of an area of atrophic normal parathyroid from around the adenoma from Patient 2. The chief cells contain large amounts of glycogen (*gl*) and lipid (*L*). There are no secretory granules or Golgi apparatuses identifiable. Extracellular spaces (*E*), nuclei (*N*), nucleoli (*n*), desmosomes (*d*), basement membrane (*B*). Uranyl acetate. Mag. 8,400 ×

large amounts of glycogen scattered through the cytoplasm, which contains only a small, inconspicuous Golgi apparatus, and small amounts of ergastoplasm. The perivascular and extracellular spaces, often large, are similar to those seen in the normal human parathyroid (MUNGER and ROTH). The cell membranes are

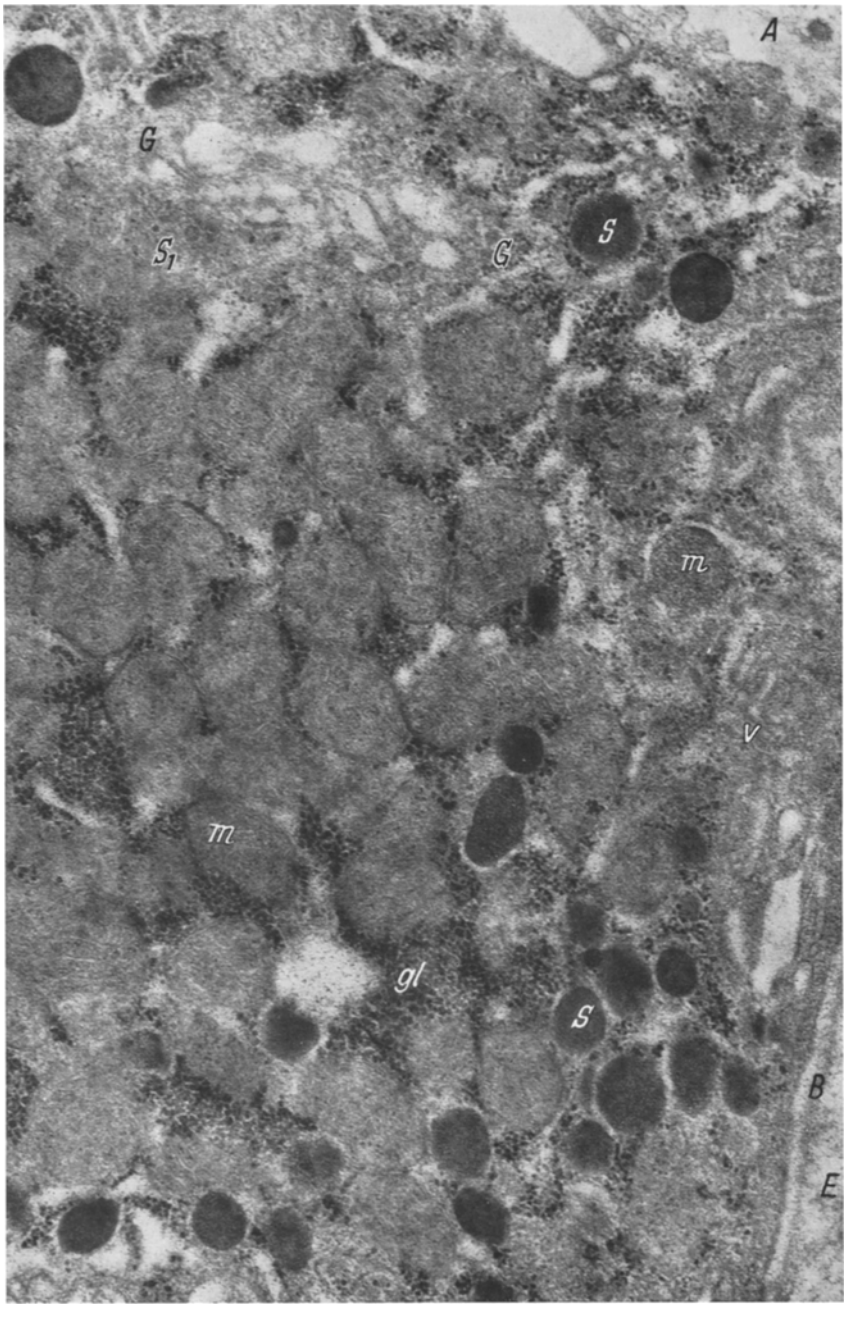


Fig. 18. Electron micrograph of an oxyphil cell from Patient 3 containing many secretory granules (*S*) and a prominent Golgi apparatus (*G*), surrounded by many smaller granules (S_1) and vacuoles (*v*) of various densities. Mitochondria (*m*), glycogen (*gl*), basement membrane (*B*), acinar lumen (*A*), extracellular space (*E*). Lead subacetate. Mag. 33,000 ×

straight and parallel or interdigitating with desmosomes connecting adjacent cells. No secretory granules are seen in the endothelial cells.

Primary Chief Cell Hyperplasias

Patient 3. The tissue from all four glands is composed almost exclusively of polygonal oxyphil cells. The cell membranes are relatively straight and parallel

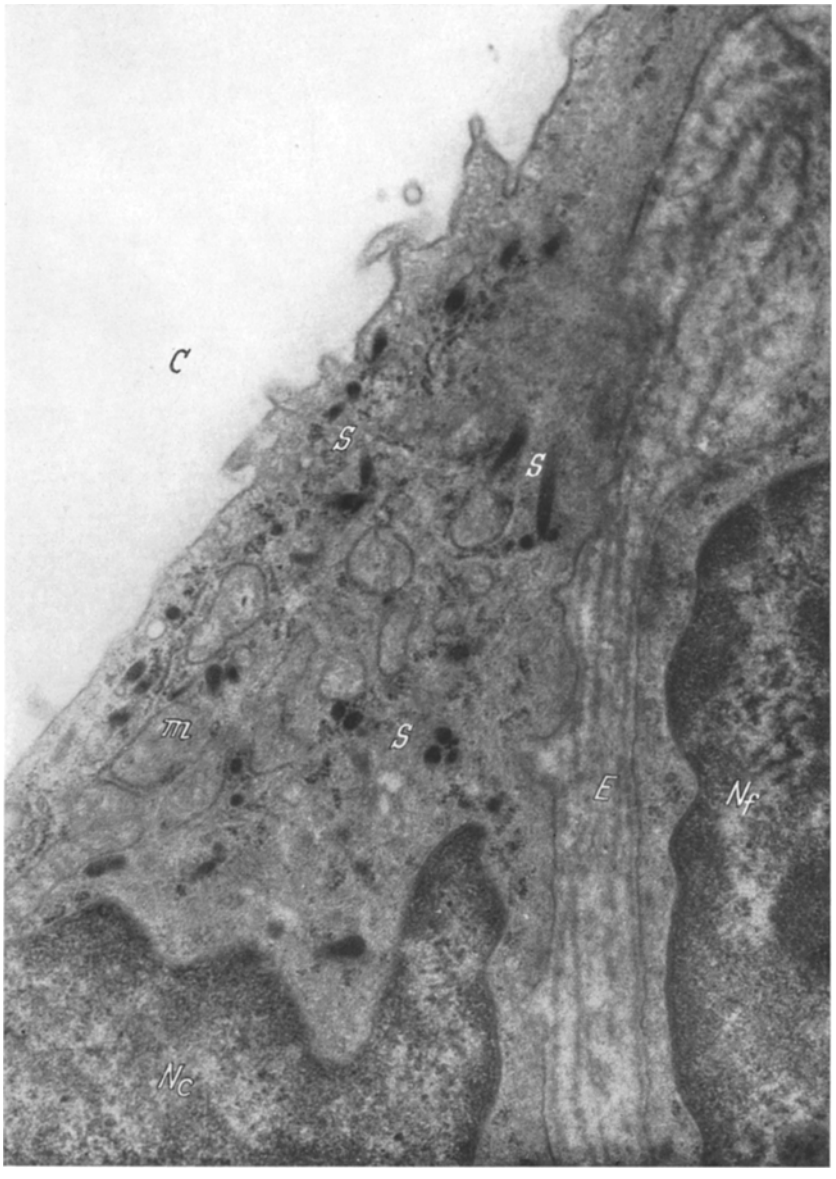


Fig. 19. Electron micrograph of a capillary endothelial cell from Patient 3 showing numerous secretory granules (*S*) in the cell cytoplasm. Mitochondria (*m*), capillary lumen (*C*), nucleus of endothelial cells (N_c), nucleus of fibroblast (N_f), extracellular space (*E*). Uranyl acetate. Mag. 22,750 ×

with only rare connecting desmosomes. In some areas the extracellular spaces are expanded, with enfolding and interdigitation of the cell membranes. The oxyphil cytoplasm is largely filled with mitochondria, the intervening spaces

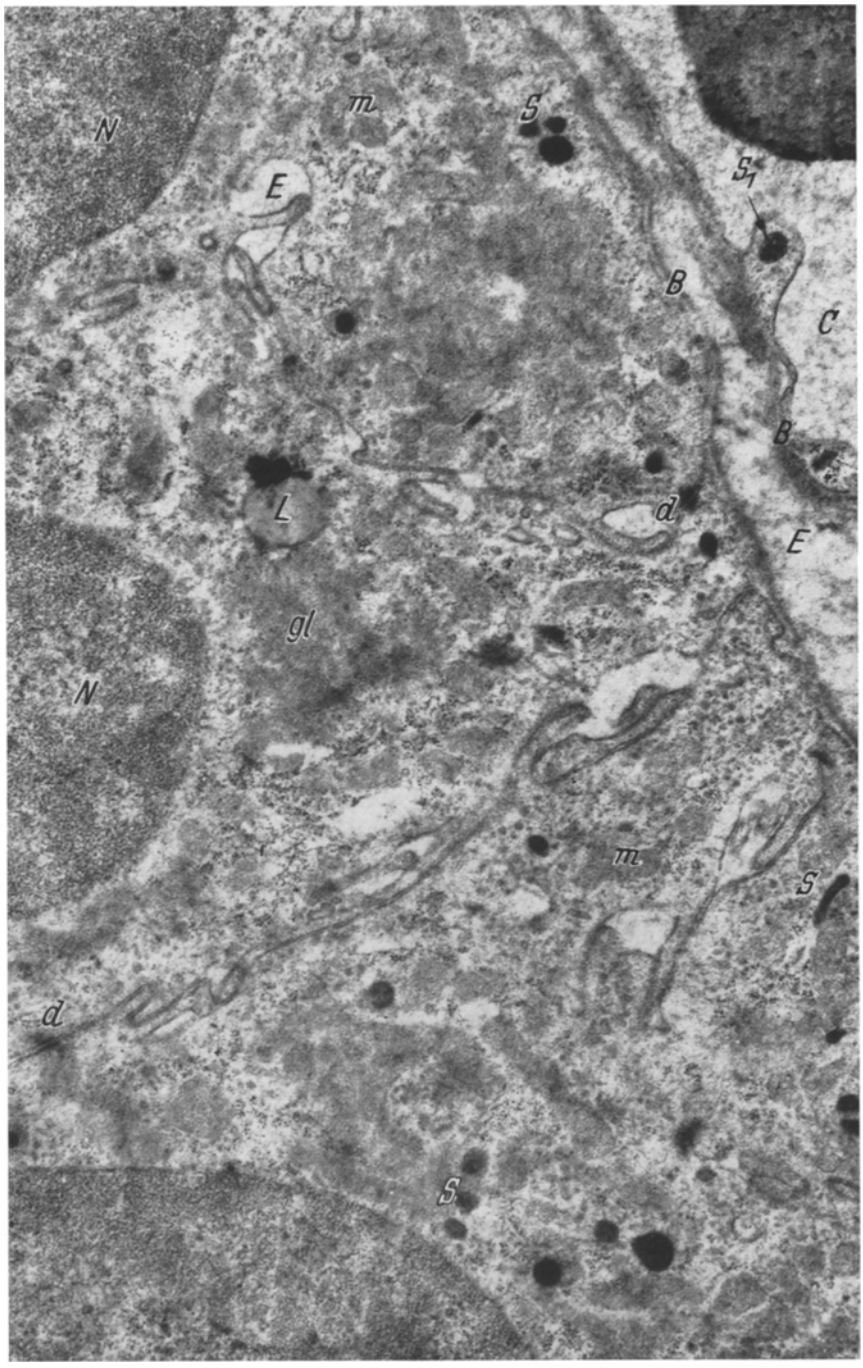


Fig. 20. Electron micrograph of chief cells and capillary (*C*) from Patient 4, primary chief cell hyperplasia. Nuclei (*N*), secretory granules (*S*), mitochondria (*m*), lipid body (*L*), glycogen (*gl*), desmosome (*d*), extracellular space (*E*), basement membranes (*B*), secretory granule (S_1) in capillary endothelial cell. Uranyl acetate. Mag. 18,000 ×

containing large amounts of glycogen. The mitochondria are identical to those of normal oxyphils. Individually and in groups are large numbers of round to rod-shaped electron-dense, membrane-lined granules (Fig. 18). These have a granular fine structure with 1 to 2 μ areas of increased density. These granules are larger than those seen in normal or adenomatous human parathyroids, but somewhat smaller than those of the Virginia deer (MUNGER and ROTH). The average size ranges from 25 to 50 mμ in diameter and 150 to 400 mμ in length. In the region of the Golgi apparatus are numerous smaller prosecretory granules of various electron densities. The Golgi apparatus is composed of parallel arrays of smooth-walled sacs and vesicles. A prominent ergastoplasm of parallel sheets of granular membranes is often present, sometimes seeming to surround the nucleus or to form a perinuclear cap. The cytoplasm contains occasional round lipid bodies, sometimes multilocular. The nuclei are similar to those of normal oxyphil cells and of chief cells.

The extracellular spaces are occasionally expanded and appear continuous with the areas in the center of the acini. Some terminal bars are seen at the edges of the acini. The perivascular spaces are wide. A basement membrane is applied to the connective tissue side of both the capillary and endothelial cells and the oxyphil cells. The spaces contain fibroblasts, collagen fibers, and unmyelinated nerve fibers.

The capillary endothelial cells (Fig. 19) often contain membrane-lined electron-dense secretory granules, identical in internal structure, size, and shape to those granules in the parathyroid epithelial cells.

Patient 4. The tissue from all four glands is composed of polygonal chief cells, similar in structure to normal chief cells (Fig. 20). The secretory granules are larger than those of the normal chief cell and much more numerous. In size, shape, and structure they resemble the secretory granules in the parathyroid cells of Patient 3. The fixation of these glands was not optimal, and the intracytoplasmic membrane systems of the mitochondria and Golgi apparatuses are poorly preserved. In occasional cells a well-formed Golgi apparatus can be identified, and associated with it are numerous prosecretory granules and vacuoles. The glycogen content of these cells as well as the amount of lipid is noticeably less than that of the normal chief cell, or of the chief cell of the parathyroid adenomas. Desmosomes connecting adjacent cell membranes are frequent. The perivascular and extracellular spaces are large. A well-formed basement membrane surrounds the epithelial cells and the capillary endothelial cells.

The endothelial cells contain numerous secretory granules, identical to those in the chief cell. In some cases the granules are in fingers of cytoplasm that bulge into the capillary lumen (Fig. 20) as if they were in the process of being extruded. Rarely a secretory granule is seen in the connective tissue stroma between the chief cells and the capillary endothelial cells.

Discussion

The identification of the secretory granules in electron micrographs of the normal parathyroid gland of man and Virginia deer by MUNGER and ROTH and their establishment as the hematoxylin-positive bodies of GRAFFLIN (1) and the argyrophilic granules of WEYMOUTH and BAKER allow study of the degree of

parathyroid secretion. Though the development of these granules from the pro-secretory granules and vacuoles in the Golgi region has not been absolutely proved, the identification of small membrane-limited granules of various sizes and densities indicates a possible developmental sequence. The electron density of these granules is similar to that found in other polypeptide- and protein-containing secretory granules, such as the α- and β-cells of the pancreatic islets [MUNGER (1)]. Fractionation of bovine parathyroid tissue (L'HEUREUX and MELIUS) would seem *to indicate that most of the parathyroid hormone activity is in a fraction that sediments between the mitochondria and microsomes.* This further evidence that most of the parathyroid activity is associated with a granular component of the cell has to be evaluated in terms of fractionation data for the liver (HOGEBOOM), since no electron-microscopic controls were performed in the study of L'HEUREUX and MELIUS.

Surrounding an adenoma in the rim of "normal" parathyroid, where the formation and secretion of parathyroid hormone has presumably been depressed by the elevated serum calcium resulting from the overfunctioning adenoma, all of the cells have an ultrastructure similar to that of the nonactive chief cells in normal parathyroids (MUNGER and ROTH). Though the regulatory mechanism is not clear, it is apparent that in the presence of a functioning parathyroid adenoma the normal chief cell decreases the size and extent of the Golgi apparatus, thought to be the site of "packaging" for cellular secretions in several organs (PALAY) and also decreases the amount of parathyroid hormone stored as secretory granules. In the normal parathyroid the ergastoplasm, the site of protein synthesis, is not prominent, and thus any decrease in its size or extent is not easy to identify. In the case of increased production of parathyroid hormone, as seen in both parathyroid adenomas and primary chief cell hyperplasias, however, the cells contain large amounts of ergastoplasm, as well as a large, prominent Golgi apparatus. Thus the cells able to produce large amounts of parathyroid hormone increase all of the components necessary for the synthesis of proteins and for their packaging into secretory units. The presence of large amounts of glycogen even in those abnormal cells producing secretory products indicates that the other cell processes have also escaped the normal control mechanism. In contrast to abnormal chief cells, MUNGER and ROTH demonstrated that normal parathyroid chief cells in the actively secreting phase have scant glycogen, and in the inactively secreting phase have abundant glycogen. No morphologic changes could be identified that could be interpreted as indicating the mechanism of loss of control of growth and hormone secretion. Though secretory granules were found in the capillary endothelial cells of the parathyroid adenoma and chief cell hyperplasia, only in one case were secretory granules found in the extracellular or perivascular spaces (and these granules were rare), but this is felt to be probably a matter of numbers of granules and time of transit. Secretory granules were also found in the endothelial cells of normal human parathyroids (MUNGER and ROTH) and the possibility is proposed that the secretory control might be at least partially regulated through these cells. In the atrophic parathyroid tissue surrounding parathyroid adenomas, no secretory granules were found in the endothelial cells, and it is felt that any granules stored in this location have been already secreted. Similar accumulations of secretory granules of the α-cells have been found in the

capillary endothelial cells of the pancreatic islets [MUNGER (3)], where their role in the secretory process is also unclear.

It is now clear that the dark chief cells with many secretory granules, a large Golgi apparatus, and little glycogen are the active secretory cells, and the so-called light chief cells with few secretory granules, a small Golgi apparatus, and large amounts of glycogen are the inactive secretory cells. The cytoplasm of the oxyphil cells is filled largely with mitochondria and glycogen. In the normal and the atrophic normal parathyroid gland, the oxyphil cells contain only rare secretory granules and an inconspicuous apparatus for protein synthesis and secretion. In adenomas and chief cell hyperplasia, however, many oxyphil cells contain secretory granules in addition to the mitochondria and glycogen. These are often associated with prominent ergastoplasm and Golgi apparatuses. This would seem to indicate that the oxyphil cell is a chief cell with altered metabolism that in the normal state is capable of producing some parathyroid hormone, but most of its energy-producing mechanisms (the mitochondria) are either used for other purposes or wasted. In the oxyphil cells of adenomas in which the control mechanisms have been lost, however, both the secretory granules and numerous mitochondria are found. Transitional oxyphil cells are difficult to identify because of the variation in the number of mitochondria in the chief cells and the difficulties of fixation, which result in swelling of the oxyphil cells, giving them the appearance of transitional forms. The same difficulty arises in the case of water-clear cells. No definite water-clear cells were identified by light microscopy. In one tumor, adenoma cells were identified that were vacuolated in the light-microscopic preparations and in thin sections contained a relatively electron-transparent cytoplasm. These cells had secretory granules and mitochondria but no clear-cut Golgi apparatus or ergastoplasm. The mitochondria were vacuolated, but this does not prove that the changes in the cytoplasm of these cells were not due to poor fixation.

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Summary

Light- and electron-microscopic studies of two parathyroid adenomas and two cases of primary chief cell hyperplasia have demonstrated the presence of secretory granules similar to those in normal parathyroid glands. The atrophic parathyroid around the two adenomas contained only inactive chief cells identical to those in the normal parathyroid. These cells had few secretory granules, and small Golgi apparatuses. The oxyphil cells were shown to be chief cells with an altered structure, but still capable of producing parathyroid hormone. The vacuolated chief or transitional water-clear cell was demonstrated in one adenoma. Water-clear cells and transitional oxyphil cells were not clearly demonstrated. Other ultrastructural features of parathyroid adenomas and primary chief cell hyperplasias were demonstrated.

Zusammenfassung

In zwei Epithelkörperchenadenomen und in den Epithelkörperchen von zwei Patienten mit primärer Hauptzellhyperplasie (Cope) konnten sowohl lichtoptisch mit der Bodianfärbung, wie elektronenoptisch Sekretgranula nachgewiesen werden. Dagegen enthielt das atrophische Drüsenrestgewebe am Rande der zwei Adenome nur inaktive Hauptzellen, die mit denjenigen normaler Epithelkörperchen übereinstimmten. Sie enthielten nur wenige Sekretgranula und einen nur kleinen Golgiapparat. Die oxyphilen Zellen sind modifizierte Hauptzellen, denen immer noch die Fähigkeit Parathormon zu sezernieren, zukommt. Das eine der Adenome enthielt vacuolisierte Hauptzellen und Übergangsformen zu den wasserhellen Zellen. Voll entwickelte wasserhelle Zellen und Übergangsformen zu den oxyphilen konnten dagegen in den Adenomen nicht mit Sicherheit nachgewiesen werden.

Es wird eingehend die Ultrastruktur der epithelialen Zellen in den Epithelkörperchenadenomen und bei primärer Hauptzellhyperplasie beschrieben.

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