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Ultrastructure of Parathyroid Adenomas*

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ABSTRACT

The ultrastructure of 12 cases of parathyroid adenomas is analyzed in the light of recent discoveries of biochemical functions of the parathyroids. Variants of parathyroid chief cells forming the adenomas are illustrated and cytologic details are explored. The correlation of cytoplasmic structures with hormone synthesis, transfer, secretion and intracellular lysosomal degradation is reviewed. A hormone secretory cycle in parathyroid adenomas is not observed. Current knowledge of parathyroid biochemistry does support modulation of hormone production and degradation by parathyroid chief cells rather than a cyclic secretory activity. Unusual structures and alterations of the normal organelles found in parathyroid adenomas are described and illustrated. Contrary to detailed knowledge of hormone synthesis, little is known about other metabolic and structural alterations in these adenomas. The reasons for massive accumulation of lipid, glycogen and mitochondria remain to be explored. As yet, neither ultrastructural investigation nor better understanding of biochemical processes of hormone production have led to recognition of etiologic factors inducing parathyroid adenomas.

Introduction

Enlarged parathyroids with associated hyperparathyroidism continue to challenge surgeons and pathologists. In primary hyperparathyroidism, differentiating adenoma from chief cell hyperplasia, be it diffuse or nodular, may be difficult at the time of surgery. It was suggested[26] that any single parathyroid weighing over 60 mg or the total weight of four parathyroids over 135 mg is suspicious of adenoma or of hyperplasia. The diagnosis of adenoma may be considered justified if a compressed normal or "atrophic" rim of parathyroid tissue is formed next to the tumor, if the other parathyroids are visualized and are found "normal in size" and at least one of those is established by biopsy and histologic examination to be of normal parathyroid tissue and, after removal of the tumorous gland, no hypercalcemia develops within two years. The reported frequency of parathyroid adenoma is 82 percent in a large series of cases of primary hyperparathyroidism. Hyperplasia is found in about 15 percent and car-

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cinoma in 3 percent of the cases.[7] One form of hyperplasia, the water clear cell hyperplasia, can be differentiated from clear cell adenomas on the basis of ultrastructural demonstration of nonglycogen containing cytoplasmic vacuoles in water clear cells.[1,2,3,4,5,6,25]

Carcinomas are recognized by their histologic characteristics. Mitoses are pathognomonic of carcinoma, as no glandular epithelial cells in mitosis are encountered in adenomas or hyperplasias.[1]

The ultrastructure of normal and pathologic parathyroid glands was described many years prior to knowledge of the biochemical mechanism of parathyroid hormone (PTH) synthesis and secretion.[1,2,4,12,23,24,27]

Analogy with animal models and with functions of other endocrine glands resulted in elaborate schemes to correlate structure with synthetic and secretory function. The biochemical findings now permit a more precise correlation and represent major progress in parathyroid physiology.

The past few years have witnessed development of immunoassays specific for PTH and for proparathyroid hormone.[18,19] Complete sequencing was accomplished of the human and several animal parathyroid hormones and of their precursors.[8,11,16] Radioautographic studies have permitted localization of newly secreted hormonal polypetides in subcellular organelles, and time sequence studies permitted observation of their intracellular migrations.[9,10,14,20,21,22]

In this report on the ultrastructure of human parathyroid adenomas it is proposed to review the cytoplasmic organization, the structures correlated with hormone production and degradation in parathyroid adenomas and note observations on unusual structural variations. The ultrastructure of parathyroid adenomas shows great variation from case to case and according to cell types. In addition to quantitative variation of normal structure, morphologically abnormal cytoplasmic organelles may be encountered. To illustrate some of the findings, 12 cases of adenomas have been selected from the files of St. Joseph's Hospital.

Clinical Material and Methods

Summary of clinical information in the 12 cases of putative parathyroid adenomas is summarized in table I. The follow-up period of two to nine years satisfies criteria for diagnosis in the first six cases. The last six cases have been followed more than one year, but less than two years; otherwise, they also satisfy parameters previously mentioned: presence of compressed remnant of "normal" parathyroid, identification of other parathyroids as "normal" with biopsy of at least one additional gland and normocalcemia postoperatively.

Tissue from the parathyroids was fixed in glutaraldehyde without delay after surgery and it was processed by standard methods for electron microscopy and for histologic examination. All of the adenomas were single and all cases were in female patients. The age ranged from 22 to 79 years at time of surgery. In two cases, the adenomas were intrathymic and required approach through the sternum.

Cytology of Parathyroid Adenomas

The cellular unit of the parathyroid parenchyma is the chief cell. The chief cells synthesize and secrete the hormone. Cytologic variations of chief cells in normal glands are the light and dark chief cells. In the light chief cells, the cytoplasmic organelles are separated further than in the dark cells by a diffuse intermixing of glycogen with the microsomal elements, thus giving the cytoplasm a lighter appearance both by the light and by the electron microscope. With aging, some chief cells enlarge and accumulate mitochondria in the cytoplasm. These

TABLE I

SUMMARY OF CLINICAL DATA

		ADENOMA			PREOPERATIVE			POSTOPERATIVE		
Case	All Females Age	Weight mg	Location	Cell Type	Renal Stones	X-Ray Bone Changes	Serum Calcium mg%	Serum Calcium mg%	Follow-Up Time	Comments
1	63	2738	Lt. Super.	Dark Chief	+	+	13.4	9.4	9 yrs.	Normocalcemic; Died, renal ins.
2	22	1200	Thymic	Dark Chief	+	–	14.8	8.7	9 yrs.	Well Normocalcemic
3	57	4500	Lt.Infer.	Chief Cells Lipid Vacuoles	–	+	14.0	8.5	8 yrs.	Severe angina & hypertension normocalcemic
4	65	2495	Lt.Infer.	Oxyphil	–	–	12.7	9.3	5 yrs.	Normocalcemic, Well
5	52	1700	Rt.Super.	Oxyphil	+	–	12.2	9.3	2 yrs.	Normocalcemic, Thyrotoxic
6	30	977	Rt.Super.	Small Clear	+	–	12.0	8.0	2 yrs.	Normocalcemic
7	72	1820	Rt.Super.	Oxyphil	–	–	11.5	9.3	1 yr.	Normocalcemic
8*	75	5600	Lt.Infer.	Small Clear	–	+	13.5	8.6	1 yr.	Normocalcemic
9	51	150	Thymic	Mixed, Dark Chief & Clear	+		11.5	8.5	1 yr.	Normocalcemic
10	79	1070	Rt.Infer.	Small Clear	–	+	12.1	7.6	1 yr.	Normocalcemic
11	36	900	Rt.Super.	Light & Dark Chief	+	–	11.1	8.4	1 yr.	Normocalcemic
12	53	1752	Rt.Infer.	Clear Cell	–	–	12.5	9.3	1 yr.	Normocalcemic

*Case 8 Preoperative serum immunoreactive parathyroid hormone level 9647 phento-moles.
Case 1 and Case 6 – Preoperatively peptic ulcer disease.
Case 1 postoperatively developed acute gout.

All patients listed in table I have completed a two year postoperative follow-up period and remain normocalcemic.

cells, referred to as oxyphil cells, form small islands in the normal gland and have a granular acidophillic cytoplasm by light microscopy. The many mitochondria may obscure the presence of hormone (protein) synthesizing organelles. These same cell types, both hypertrophied and hyperplastic, are recognizable in adenomas and in chief cell hyperplasias. In adenomas and chief cell hyperplasias, the additional glycogen accumulation may be massive, with glycogen alone occupying large portions of the cytoplasm, displacing the cytoplasmic organelles and giving a clear appearance to the cytoplasm by light and by electron microscopy. These cells are referred to as clear cells or small clear cells in distinction to the large or water clear cells encountered in diffuse clear cell hyperplasia of the parathyroids. The water clear cells contain a vacuolated cytoplasm. The 200 to 500 μm membrane-bound vacuoles have a water clear content other than glycogen. The chief cells in the normal gland are rather small from 7 to 10 μm. In hyperplasia and in adenomas these cells enlarge to 20 μm and the clear cells up to 35 μm. Water clear cells are reported[25] to measure up to 40 μm. Clear cytoplasmic appearance by light microscopy occasionally is due to an accumulation of lipid vacuoles rather than to glycogen. Small lipid vacuoles are seen to intermix with cytoplasmic organelles throughout these cells. All of the chief cells and their variations in addition contain varying numbers of secretory granules, lysosomes and lipid bodies.

In adenomas, the entire adenoma may be formed of dark and light chief cells or any of the other variant cell types. One of the cases (Case XI) is of a classical chief cell adenoma with dark and light chief cells side by side. Both of these cell types contain prominent protein secretory apparatus. Often, more than one cell type is present in the adenoma.

Three types of light chief cells were encountered in our material. First, in three cases (Cases VI, VIII and X), large areas of the cytoplasm appear empty or slightly and uniformly gray. These spaces contain PAS (periodic acid-Schiff) positive material digestible with diastase and are considered unstained glycogen accumulations by electron microscopy (figures 1 and 2). In earlier studies, this cell type was referred to as vacuolized chief cells.[1] Second, as in Case XII which is histologically a clear cell adenoma of large cells measuring 25 to 45 μm in diameter, the cytoplasm is completely filled with glycogen granules (figures 3 and 8). This cell type is classified as clear cell rather than water clear cell owing to the glycogen content and the lack of multiple clear membrane-bound vacuoles. Third, the light appearance of the cytoplasm in one case (Case III) is entirely due to accumulation of lipid vacuoles (figure 4).

Mitochondria are present in all adenoma cells, but in oxyphil cells they dominate the cytoplasm. Examples of adenomas predominantly of oxyphil cells intermingled with transitional oxyphils are our Cases IV and VII. Little or no glycogen and minimal content of lipid vacuoles are present. The mitochondria show the usual cylindrical or round profile on section, but in some mitochondria large electron dense spherical deposits are present. The cell nuclei are spherical, with one or two nucleoli. The nuclear chromatin is variable from uniform finely granular distribution to rough clumped chromatin deposited along the nuclear membrane. Double nucleated cells are frequent (figure 5).

The parenchymal cells abutt upon the perivascular space at least by one cell surface, and groups of cells nestle between capillaries. A lobular pattern or sheaths of cells occasionally with an acinar arrangement are often present. The cells are separated from the perivascular space by a basement lamina. Between cells are desmosomes, and the space is filled with a rather electron dense homogeneous mate-

rial similar to that formed in the occasional acinar lumen. Microvilli are seen to extend into both the acinar and intercellular spaces.

The vascular stroma that supports the parenchymal cells is rather inconspicuous by light microscopy. By electron microscopy, the endothelial lining is of the fenestrated type. Between the endothelial basement lamina and that of the epithelial cells, a space of uniform relatively low electron density is seen to contain a few collagen fibers, cellular extensions of fibroblasts and occasionally unmyelinated nerve fibers. These spaces are considerably widened in larger adenomas with degenerative changes and cysts.

Structures Correlated With Hormone Production

In table II are summarized the known events of hormone production. The rough endoplasmic reticulum (RER) is the site of polypeptide synthesis (figure 9). The precursor of parathyroid hormone (PTH) is synthesized on the ribosomes as a translational product of the specific mRNA. The first 25 sequences referred to as "presignal sequences" lead the polypeptide molecule into the cisternal space of the RER where the leader sequence is removed by a membrane associated peptidase.[16] The lumen is reached by the proparathyroid hormone. The proPTH contains a basic hexapeptide sequence, the "pro" sequence which precedes the aminoterminus of the hormone.[14]

TABLE II

ORGANELLES KNOWN TO PARTICIPATE IN HORMONE PRODUCTION

ORGANELLE	FUNCTION	PRODUCT
Nucleus:	TRANSCRIPTION	mRNA
Ribosomes-ER	TRANSLATION	Pre-ProPTH
ER-Membrane	SPECIFIC PEPTIDASE	ProPTH
ER-Cisternae	TRANSFER TO GOLGI	
Golgi Complex	TRYPSIN-LIKE ACTIV. CARBOXYPEPTIDASE-B	PTH
Golgi Vesicles	PACKAGING	Sec. Granules
Lysosomes	DEGRADATION	Aminoacids
Mitochondria	ENERGY FOR TRANSFER	
Microtubules	?	

The proPTH is transported through the cisternal system and possibly by vesicles derived from it into the Golgi complex. This transport is separately regulated from the synthesis and is energy dependent. The pro-hormone reaches the Golgi complex in about 15 minutes.[11] A membrane associated proteolytic activity splits the hexapeptide "pro" sequence off the proparathyroid hormone which is encased in the Golgi vacuoles. First, these vacuoles are large and contain relatively little electron-dense material and are referred to as pro-secretory granules (figure 9, arrow).

Later, the vacuolar envelope retracts around the denser secretory material and forms the secretory granule containing the PTH. These are argentophylic but are acid phosphatase negative. The granules are pleomorphic and vary from 100 to 500 μm. They migrate to the periphery of the cell where they may be expelled into the extra-cellular space by exocytosis or they may be intercepted by lysosomal bodies (figure 10). Lysosomes identified by their acid phosphatase activity are found as 400 to 900 μm irregularly shaped electron-dense membrane-bound organelles. Lysosomal degradation of secretory granules is under control of calcium ion concentration. Lysosomal bodies fuse with secretory granules and effect a degradation of the PTH.[15,28] Additional structures that may play a part in the transport of pro-hormone are microtubules suggested by enzyme inhibition studies.[9,14,20] Ultrastructural localization of pro-hormone and PTH was accomplished by radioautographic and combined chemical ultrastructural methods.[11,21]

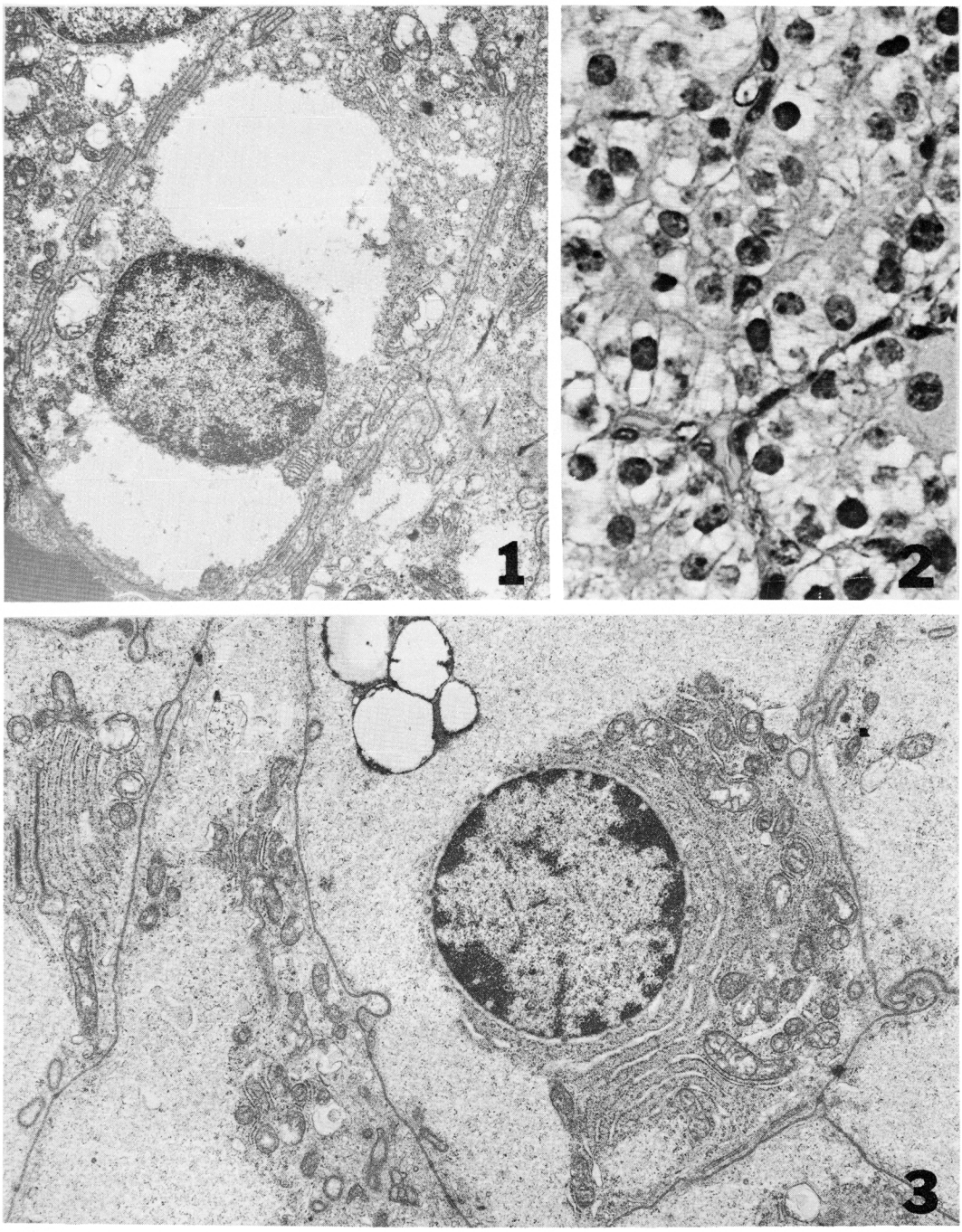
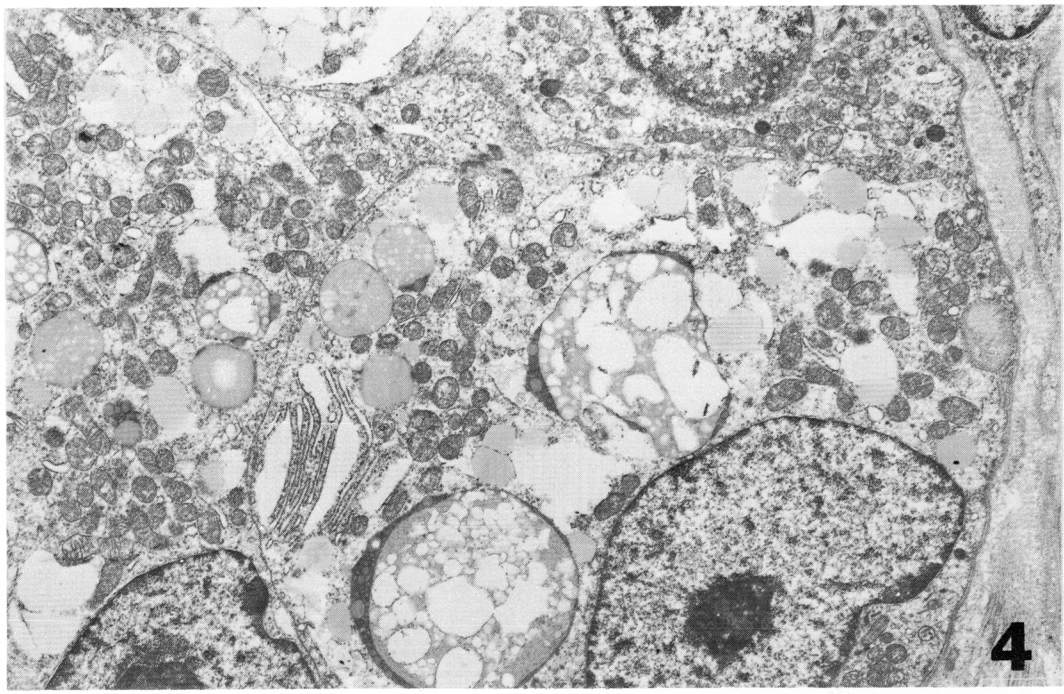


FIGURE 1. Small clear cell. Cytoplasmic organelles are displaced by unstained accumulation of glycogen. (Case 6). × 6400. Figure 2. Parathyroid adenoma. Small clear cells, histologic section, H and E. (Case 6). × 450. Figure 3. Portion of clear cells with massive accumulation of glycogen granules. Note the juxta-nuclear parallel arrays of rough endoplasmic reticulum (RER) and mitochondria. (Case 12). × 8400.



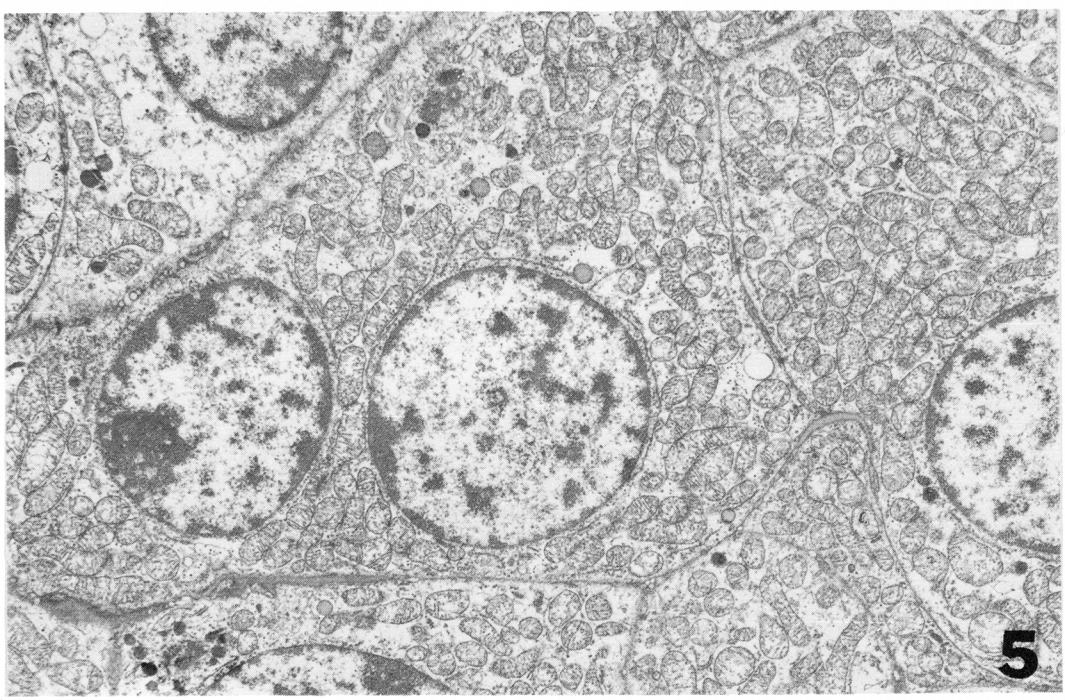


FIGURE 4. Clear cells with accumulation of lipid bodies. (Case 3). × 3500. Figure 5. Oxyphil cells. Mitochondria fill the cytoplasm. Secretion granules and lysosomal bodies are present. (Case 4). × 3000.

In all parenchymal cells of parathyroid adenomas, organelles identified with hormone synthesis, transfer, packaging and secretion are present and are usually more prominent than those seen in normal parathyroid cells. A hormone secretory cycle cannot be identified in human adenomas and hyperplasias. In parathyroids of parturient cow and in other species, parathyroids under special experimental conditions were considered to have specific morphologic appearances associated with various phases of secretory activity.[28]

Efforts to correlate serum immunoreactive parathyroid hormone concentration with secretory activity of adenomas are fraught with difficulties. One is the problem of specificity of the antiserum in the presence of immunoreactive fragments of PTH. Another is the rapid degradation of PTH with a half life of about four minutes. The biosynthesis of PTH was recently reviewed by Habener and Potts.[16]

It is considered that about one-fifth of the total biosynthetic activity of the parathyroid is devoted to hormone synthesis. The rate of hormone synthesis is ultimately regulated by the calcium concentration in extracellular fluid. Low calcium levels were found to increase PTH secretion up to five fold[13,17] and high plasma calcium levels over 11 mg per 100 ml were found to reduce PTH secretion to a minimal but significant basal calcium-independent secretion rate. Intracellular degradation of hormone by lysosomal enzymes was shown to be calcium-sensitive in *in vitro* studies. Normally, more PTH is manufactured by the glands than is required for maintenance of the normocalcemic state. The excess hormone is degraded within the cells. High concentration of calcium stimulate and low calcium concentrations inhibit lysosomal degradation of the hormone.

With the maximal PTH secretion being limited to about five times the normal secretory rate, hypertrophy and hyperplasia are of necessity the glands' response to persistently low levels of calcium in extracellular fluid as in secondary hyperparathyroidism.

An important array of cytoplasmic organelles participate in hormone production. Just as important, however, a list may be drawn of other structures not known to participate in hormone production. In pathologic states, these may eclipse the hormone secretory apparatus to a large extent as does accumulation of lipid, glycogen and mitochondria in adenomas and hyperplasias. This of course is not surprising if it is realized that four-fifths of the parathyroids biosynthesizing apparatus is dedicated to functions other than hormone synthesis. The metabolic alterations of parathyroid chief cells outside of the hormone secretory cycle have not been systematically investigated.

Other normal cytoplasmic constituents are microfilaments at the periphery of the cells and centrioles. Intracytoplasmic cilia are occasionally encountered, but their significance, if any, is not clear.

Observations on Unusual Structures

Case VI is remarkable because of the large number of stacked annulate lamellae in the light chief cells. In addition, this case contains numerous multinucleated giant cells (figure 6). The giant cell nuclei are of irregular outline with rough chromatin pattern. The cytoplasm is dark with condensation of organelles and many mitochondria. Annulate lamellae are numerous in the giant cells as well. The origin and significance of annulate lamellae is not certain. Morphologically, these are parallel lamellar systems interrupted by numerous pores at regular intervals. They may form whorl-like or semicircular concentric arrays similar to systems of RER. Occasionally, annulate lamellae are found continuous with cisternae of RER. Another form of intracytoplasmic membrane abnormality is illustrated in figure

11. Accumulation of haphazardly oriented membrane profiles upon close scrutiny are found to consist of endoplasmic reticulum reflected upon itself retaining ribosomal granules only on its external surface, the cisternal spaces being separated only by the double layer of the smooth membrane. No description in other adenomas of this type of change has been found by us.

Mitochondria may form peculiar bodies in association with stacked parallel arrays of RER. In Case XII, many of the mitochondria appear collapsed and elongated between the parallel rough membranes of the ER. The two ends extending outside of the stacked lamellae may continue into a normal mitochondrial structure or may be seen only as cross-section of bulbous vesicles defined by the double membrane of mitochondria (figures 8 and 13). In the collapsed zone, six parallel electron dense membranes closely apposed with fine uniform sinusoidal pattern are seen on longitudinal cross-sections. Incompletely collapsed forms in transition from normal mitochondrial structure to the very condensed membranous structure are common. Incompletely collapsed mitochondria were found in another case by Thiele.[29]

Another unusual finding in Case VI is a paracrystalline inclusion in an area of the cytoplasm exceptionally rich in RER. The structure is not bound by membrane. The crystalline array show a periodicity of 20 nm (figure 12).

Rarely in the perivascular interstitium, unmyelinated autonomous nerve fibers are recognizable. In one field, a nerve ending forming synapsis with chief cells has been observed. Viral particles were not encountered, although the adenomas were carefully surveyed for their presence.

Other structures that are seen even in normal parathyroid cells may have special meaning for hyperplastic and adenomatous cells. Hormone synthesis and secretion seems independent in these cells from accumulation of lipid vacuoles, glycogen or mitochondria. In addition, the synthetic product, PTH, is the same in adenoma as in the normal secreting gland. The etiologic factors of parathyroid adenoma, on the other hand, cause massive derangements in adenoma cell metabolism expressed by the accumulation of glycogen, lipid or mitochondria, and it leads to unusual structural changes, such as the parallel arrays and concentric whorls of RER, accumulation of ER membrane structures reflected upon themselves, annulate lamellae, collapsed mitochondrial bodies, mitochondrial inclusion, intracytoplasmic cilia and paracrystalline inclusion bodies.

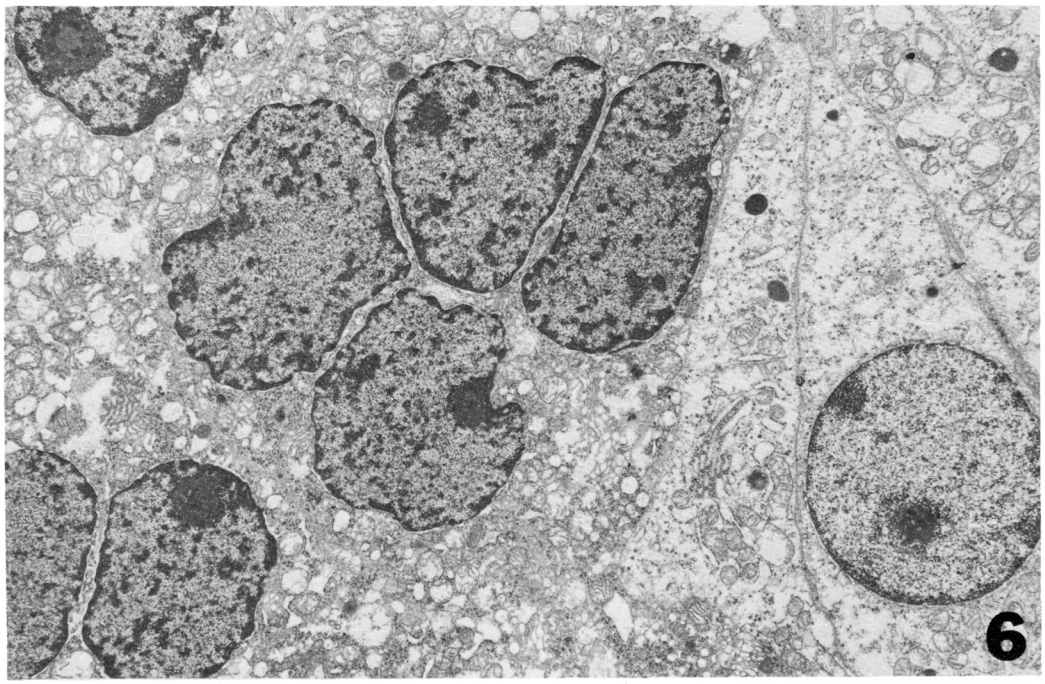
Summary

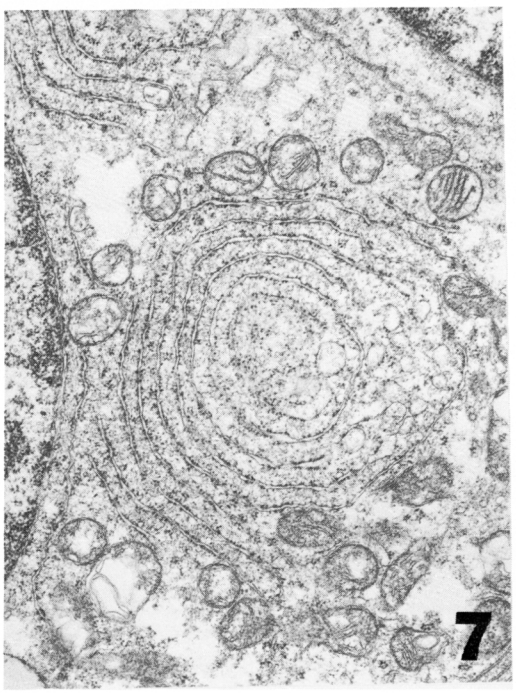
The ultrastructure of 12 parathyroid adenomas are analyzed as to cytologic description, correlation of cytoplasmic structures with hormone production and unusual structures or structural aberrations not previously reported.

Histologic criteria are precise and sufficient to separate parathyroid carcinoma from adenomas and hyperplasias. Ultrastructural criteria are sufficiently specific to separate water clear cell hyperplasia from all other forms of parathyroid abnormalities based on the presence of membrane-bound cytoplasmic vacuoles that contain no glycogen.

Diagnosis of adenoma versus hyperplasia is based on both surgical exploration and biopsy of at least one histologically "normal" parathyroid. Besides the enlarged gland, it is based on finding residual "normal" or atrophic parathyroid tissue in the tumorous gland and, on clinical follow-up, the maintenance of post operative normocalcemia for a period of two years.

Our cases include one example of chief cell adenoma formed of dark and light chief cells side by side. In our cases there are three types of light chief cells: the first due to accumulation of lipid vacuoles (Case III); the second due to partial filling of the cytoplasm with unstained glycogen





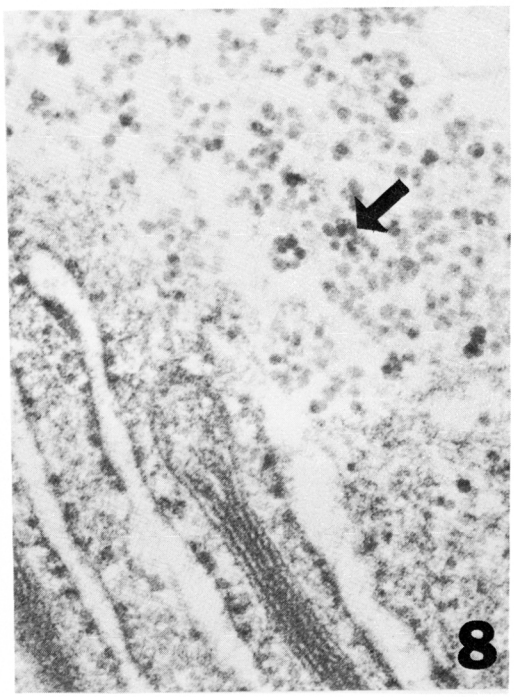
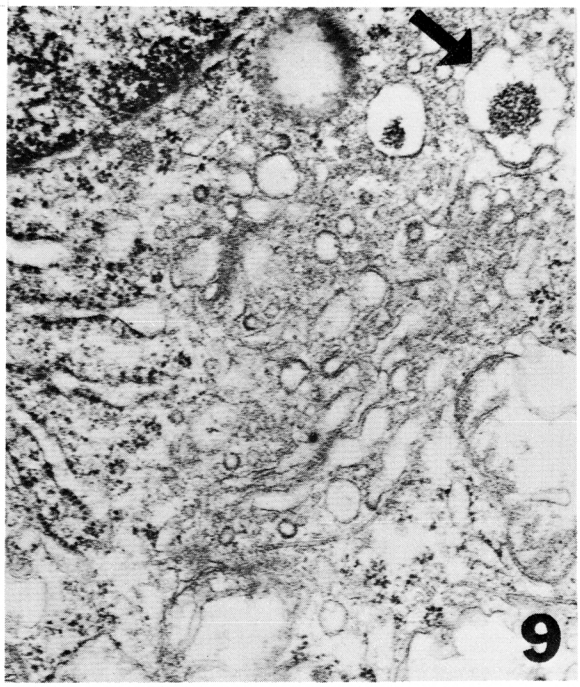
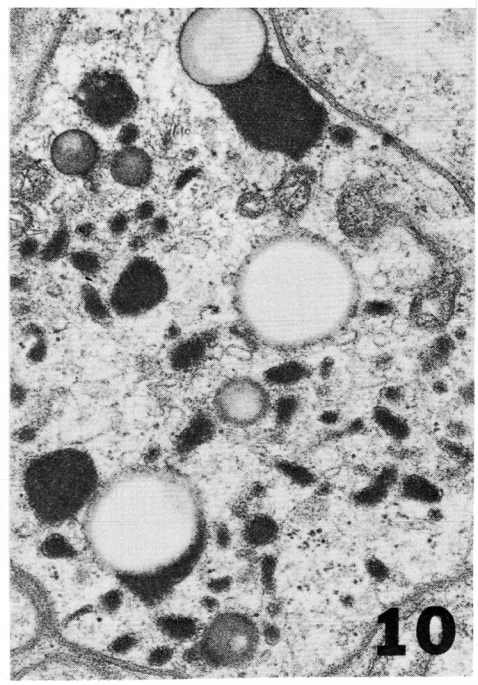
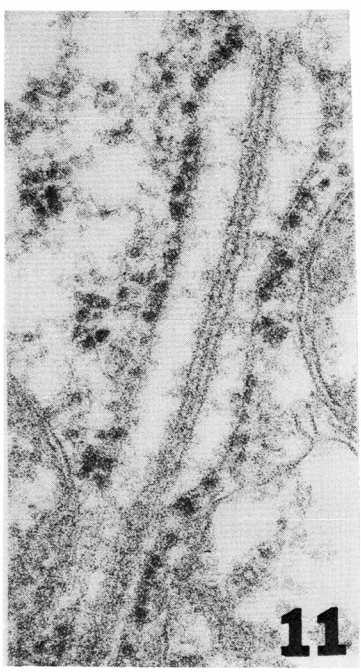
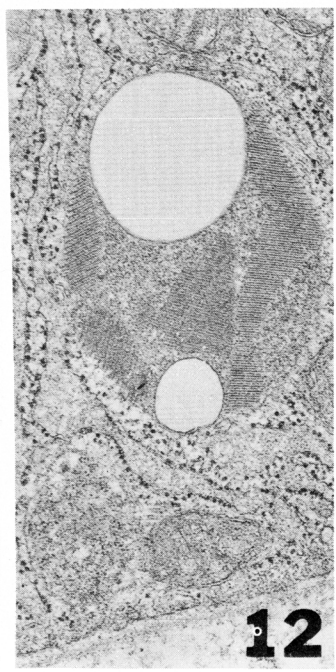


FIGURE 6. Multinucleated giant cell on left. Light chief cell on the right. Annulate lamellae rather than rough endoplasmic reticulum (RER) are present in giant and chief cell cytoplasm. Parathyroid adenoma. (Case 6). × 4000. Figure 7. Concentric lamellar body. The rough endoplasmic reticulum (RER) cysternae continue into vesicles. Parathyroid adenoma. (Case 6). × 11,200. Figure 8. Cytoplasmic detail, right upper half; glycogen granules; left lower half, stacked rough endoplasmic reticulum (RER) and collapsed mitochondrial body. (Case 12). × 74,000.









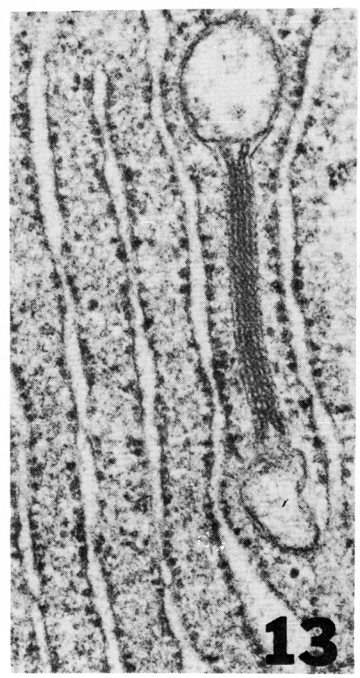


FIGURE 9. Detail of cytoplasmic organization. Rough endoplasmic reticulum (RER) on left extends to Golgi vesicles toward the center. Presecretory granules are at arrow. Parathyroid adenoma. (Case 6). × 22,500. Figure 10. Secretory granules and lysosomes, demonstrating incorporation of small dark pleomorphic secretory granules into larger lysosomal vesicles and the formation of lipid bodies. Parathyroid adenoma. (Case 12). × 23,500. Figure 11. Detail from an area of accumulated membrane profiles. Endoplasmic reticulum reflected upon itself. (Case 6). × 64,000. Figure 12. Paracrystalline inclusion in chief cell cytoplasm. (Case 6). × 20,000. Figure 13. Mitochondrial alterations in association with parallel arrays of the rough ER. Note the sinusoidal folds of membranes. Parathyroid adenoma. (Case 12). × 46,000.

(small clear cells) (three cases); and the third, a large clear cell with cytoplasm completely filled with glycogen granules (one case). Oxyphil cell adenomas are characterized by cytoplasmic accumulation of mitochondria (three cases). The remaining two cases are cytologically of dark chief cell adenomas.

There is no evidence for a hormone secretory cycle in parathyroid adenomas. Normally, more PTH is manufactured by the glands than is required for maintenance of the normocalcemic state. The excess hormone undergoes intracellular degradation by lysosomal enzymes. The organelles forming the structural basis for PTH synthesis, secretion and degradation are illustrated in the electron micrographs.

Neither ultrastructure nor perfect understanding of biochemistry of hormone production provides clues as to the etiology of parathyroid adenomas. Hormone synthesis is apparently independent in adenoma cells from accumulation of lipid vacuoles, glycogen or mitochondria. The biochemical derangement leading to these accumulations might be more informative as to etiologic factors of parathyroid adenomas than are factors of hormone secretion.

Finally, attention is called to abnormal structures in parathyroid adenomas, in addition to the previously observed annulate lamellae: intracytoplasmic cilia and mitochondrial dark inclusion bodies, rare findings of "collapsed mitochondrial bodies" associated with stacked RER, accumulation of membrane structures originating from ER reflected upon itself and finding of paracrystalline inclusions.

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