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Electron Microscopy in the Diagnosis of Pituitary Tumors

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ABSTRACT

The usefulness and limitations of electron microscopy (EM) in pituitary tumor diagnosis are reviewed and illustrated with clinical examples. The traditional classification of chromophil and chromophobe adenomas is often inconsistent with the hormonal activity of the tumors. Virtually all pituitary adenomas contain some secretory granules when viewed with EM. Endocrine inactive chromophobe adenomas contain 150 nm granules with no demonstrable hormone function. Typical growth hormone (GH) secreting eosinophil adenomas contain large 375 nm granules which dominate the cell cytoplasm. GH secreting chromophobic tumors contain secretory granules of abnormal size and concentration which are invisible to the light microscopist. The variability in granule size may indicate the production of abnormal granules or reflect the stage of the cell in a secretory cycle. Because of this wide range in granule size, the identification of tumor cell type or hormone produced is not reliable by granule measurement alone. Some neoplasms in the sella turcica may be so bizzare or undifferentiated as to defy classification. In such instances, EM can reveal ultrastructural details which identify their origin from pituitary tissue. Malignant pituitary tumors may contain minute secretory granules, and rare pituitary oncocytomas are packed with abnormal mitochondria.

Introduction

The pathology and natural history of pituitary tumors have been well described since the early part of this century when Dr. Harvey Cushing pioneered the neurosurgical techniques for the treatment of these lesions. In the traditional classification, three important types were listed: chromophobe adenomas, eosinophilic adenomas and basophil adenomas. Each was thought to be derived from a separate cell line seen in normal pituitary tissue. A variety of special stains was developed to distinguish between cell types and to identify the secretory product.

In this schema, a distinct clinical syndrome corresponded to each category of pituitary tumor. The chromophobe

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adenomas were hormonally inactive and produced symptoms of hypopituitarism by compressing normal hypophyseal tissue. Eosinophil adenomas caused acromegaly by the overproduction of growth hormone (GH), and basophil adenomas secreted excess adenocorticotrophic hormone (ACTH) with resultant Cushing's disease.

The early findings of electron microscopy (EM) tended to support this classification. In endocrinologically active cells, the cytoplasm was seen to contain large numbers of membrane bound, electron dense secretory granules, i.e., packages of hormone ready for secretion. Measurements of granule diameter seemed to indicate that the size of the secretory granules varied with the cell type and consequently with the hormone produced.[22] If this were the case, simple measurements of granule size could be used to identify the hormone contained within normal and neoplastic cells. Careful analyses indicated, however, that such an identification was difficult.

In the first place, within normal cells of the same type there was a wide range of granule size which varied with different phases of cell rest and secretory activity.[6] In the case of pituitary tumors, the picture was even more confusing. Separate authors reported a wide variety of granule sizes in adenomas of the same histologic type. Consequently, there is a concensus among pathologists that granule size alone cannot reliably be used to identify the secretory product in pituitary tumors.

Given the simplicity and success of routine histologic and histochemical methods, and given the limitations of EM, an expensive cumbersome tool, what role can ultrastructural studies play in the diagnosis of pituitary tumors? The answer to that question lies with the failure of many pituitary tumors to conform to the simple classification of chromophobe and chromophil previously outlined. Frequently, the pathologist encounters a "chromophobe" adenoma associated with acromegaly, and some tumors with granular, eosinophilic cytoplasm show no evidence of hormone production. In addition, tumors in the sella turcica can be so bizzare and anaplastic as to defy classification; in these cases, the EM may reveal ultrastructural details identifying the origin and nature of these lesions.

This communication will illustrate the usefulness of EM in several of these instances.

Materials and Methods

Specimens of pituitary tumors were obtained at the time of trans-sphenoidal hypophysectomy. Tissue for light microscopic examination was fixed in 10 percent formalin and processed by the usual methods. Sections were stained with hematoxalin-eosin (H&E), Orange-G-periodic acid-Schiff (OG-PAS) and Wilder's reticulin. Specimens for EM were fixed in 4 percent gluteraldehyde, post-fixed in 4 percent osmic acid, dehydrated in graded alcohols and embedded in Epon-12. Sections were cut on a LKB-III ultramicrotome using a diamond knife, stained with lead citrate and uranyl acetate and examined with a Philips electron microscope using an acceleration voltage of 80 kV.

Non-functioning Chromophobe Adenoma

Chromophobe adenomas are reported to be the most common of pituitary tumors, accounting for up to 79 percent in older series.[19] They usually present no diagnostic problem to the pathologist. Typically, the normal architecture of the gland is replaced by cells in a diffuse or sinusoidal pattern with ill defined agranular cytoplasm and no affinity for special stains. A chromophobe adenoma from a 69 year old man with a two year history of reading difficulty is illustrated in figure 1. A bitemporal hemianopic visual field de-

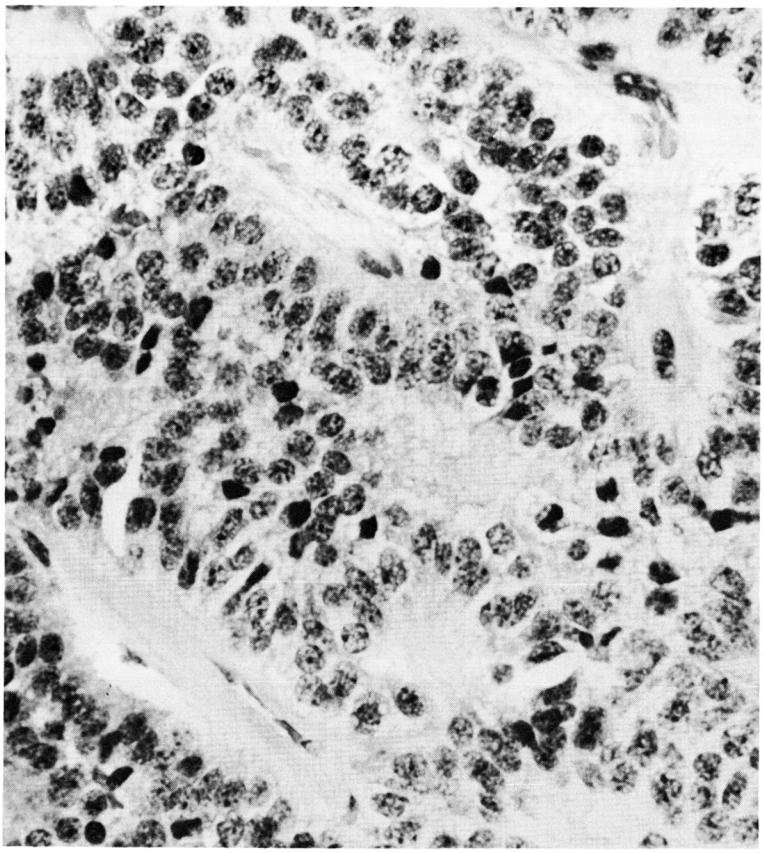

FIGURE 1. Endocrine inactive pituitary adenoma. Sinusoidal pattern. The cytoplasm is agranular and chromophobic (H&E × 250).

fect was found on neurologic examination. Polytomograms showed enlargement of the sella turcica. No endocrinopathy was demonstrated by clinical laboratory tests. The histologic pattern is sinusoidal; the cytoplasm is agranular and unstained.

An electron micrograph from this tumor is illustrated in figure 2. The nuclei are lobulated and pleomorphic, and prominent nucleoli are present. The cell membranes are closely applied and interdigitated, but no desmosomes are noted. There is a rich assortment of cytoplasmic organelles including numerous oval or elongated mitochondria and stacks of rough endoplasmic reticulum. Small dense granules are scattered throughout the cell sap, especially along the plasmalemma. These granules measure 100 to 150 nm in diameter and are surrounded by a unit membrane. They are similar in size and distribution to granules seen in "chromophobe" cells of the normal pituitary gland.[18]

At one time it was believed that the chromophobes of the anterior pituitary were non-functioning, multipotential stem cells waiting in reserve; eventually they would become active chromophils as the latter were lost by attrition or in response to some metabolic demand. It is now known that this notion is too simple. With careful attention to the technical details of fixation it can be shown that virtually all chromophobe adenomas have some degree of granulation seen by both light microscopy and EM.[15] Furthermore, a combination of immunohistochemistry and EM revealed that chromophobes in the anterior pituitary were actively secreting a variety of hormones. Most are responsible for ACTH production, but other

chromophobes may secrete thyrotropin or gonadotrophic hormones.[6]

The nature and significance of the granules in chromophobic tumors are the subject of much interest and speculation. In terms of their size and configuration, they are similar to granules seen in ACTH, thyrotrophic hormone, follicule stimulating hormone and leuteotrophic hormone producing cells.[4,11] Nevertheless, most patients with chromophobe adenomas have clinical signs of hypopituitarism rather than those of excess hormone secretion. Olivier et al have reviewed some of the theories accounting for the problem of secretory granules in tumors with no evident endocrine function.[17] It is possible that the tumor produces a secretory granule which is abnormal and, therefore, has no biological activity. Alternatively, the granules are not secreted but destroyed *in situ*. The latter possibility is unlikely, since there are several convincing demonstrations of exocytosis of these granules into the extracellular and perivascular spaces.[4,25]

Acidophil Adenoma With Acromegaly

Tumors producing acromegaly account for 10.7 to 32 percent of all pituitary

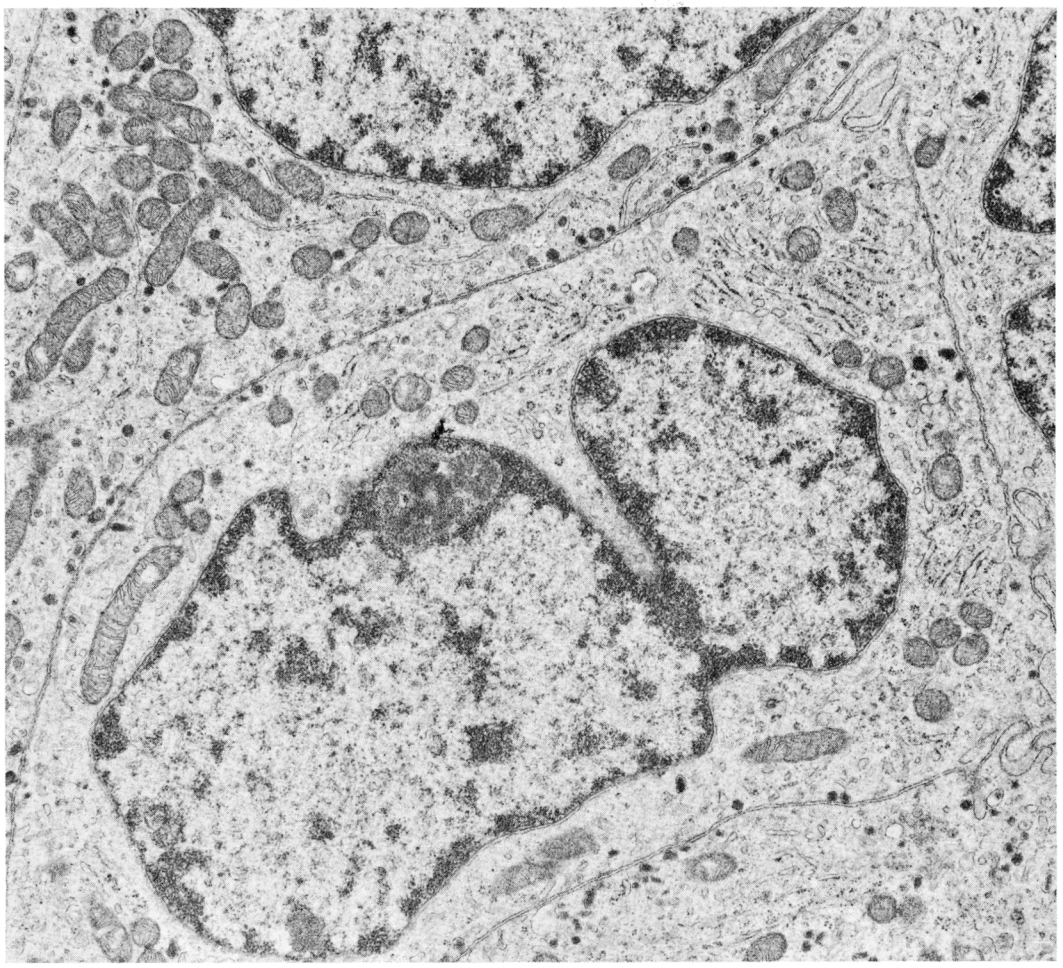

FIGURE 2. Endocrine inactive adenoma. A few dot-like secretory granules are concentrated along the cell membranes (× 13,000).

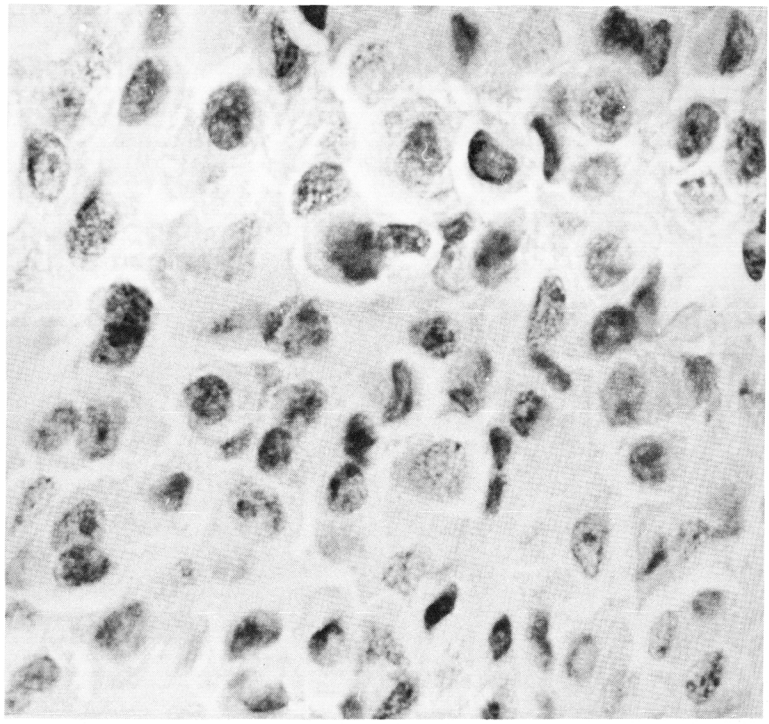

FIGURE 3. Growth hormone secreting pituitary adenoma. Diffuse pattern. The cytoplasm is granular and stains brilliantly with eosin and orange-G (H&E × 400).

neoplasms depending upon the series, the higher figures coming from referal centers with active neurosurgical services.[8,11] Several reviews of their light microscopic and EM characteristics have already been published.[12] Typically, tumor cells have abundant cytoplasm filled with brilliant eosinophilic granules which can be demonstrated to contain GH by a variety of techniques including immunofluorescence and immunohistochemistry.[16,24] Such a tumor is shown in figure 3 from a 45-year-old woman with a two year course of amenorrhea, coarsening of facial features and enlargement of the jaw, tongue and hands. The serum GH level was 162 ng per ml (normal is less than 10 ng per ml). Tumor cells seen by light microscopy are arranged in a diffuse pattern (figure 3). The individual cells are large and oval with some nuclear pleomorphism. The cytoplasm is densely granular and stained intensely with eosin and Orange-G.

There is good correspondence between the light microscopic and ultra-strucutral characteristics of the lesion. In figure 4, EM shows considerable nuclear infolding and lobulation. The cytoplasm is dominated by large prominent osmiophilic granules to such an extent that the other cytoplasmic organelles are obscured. This is in marked contrast to the scattered dot-like granules seen in the "non-secreting" chromophobe adenoma. The granules measure up to 600 nm with an average diameter of 375 nm. These values correspond well to granule size measurements made in normal human somatotrophic cells and in other GH secreting eosinophil adenomas.

It is appropriate at this point to interject a note of caution. Similar size ranges are found for secretory granules in other types of pituitary tumors, including those producing ACTH and prolactin.[3,13] Consequently, there is nothing unique about granule size in neoplastic cells, and the identification of cell type or hormone by granule measurement is unreliable without other ancillary data.

Chromophobe Adenoma With Acromegaly

How the traditional classification of pituitary tumors frequently breaks down is illustrated in the following example. A 26-year-old woman presented at the emergency room of the Downstate Medical Center with complaints of persistent headache and blurred vision following a head injury sustained four weeks previously. A routine skull x-ray revealed enlargement of the sella turcica with erosion of its floor.

General physical and neurological examination were unremarkable, but on careful questioning the patient admitted to an increasing shoe size over the last few years. Endocrinological evaluation demonstrated elevated GH levels (101 ng per ml), and radiographic studies showed alterations in the mandible and extremities consistent with acromegaly. A pituitary tumor was removed by a trans-sphenoidal approach. A light microscopic view of the lesion is seen in figure 5.

The tumor destroyed the floor of the sella turcica and bulged into the sphenoid sinus. The bony wall is completely gone, and only a thin rim of connective tissue separates the tumor from the respiratory

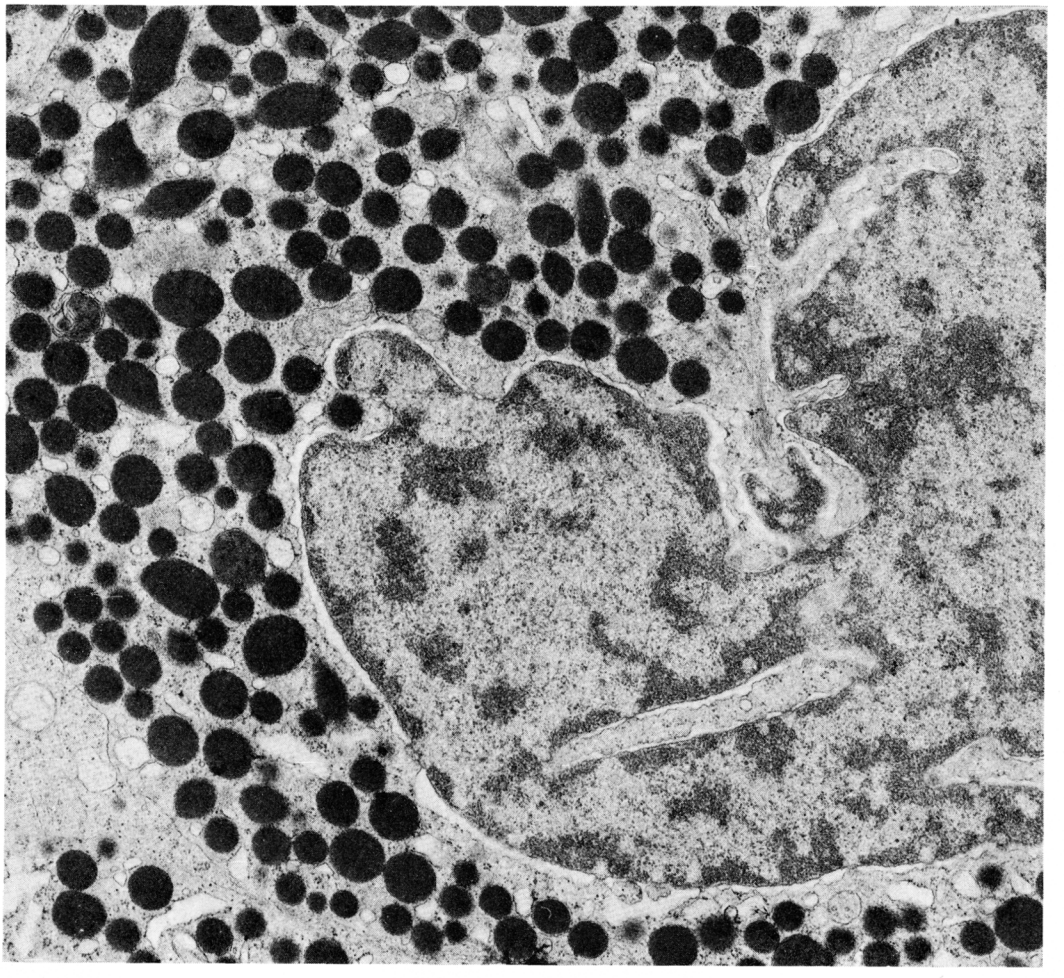

FIGURE 4. Growth hormone secreting pituitary adenoma. Large, electron dense secretory granules dominate the cytoplasm. They measure 375 nm in average diameter (× 14,000).

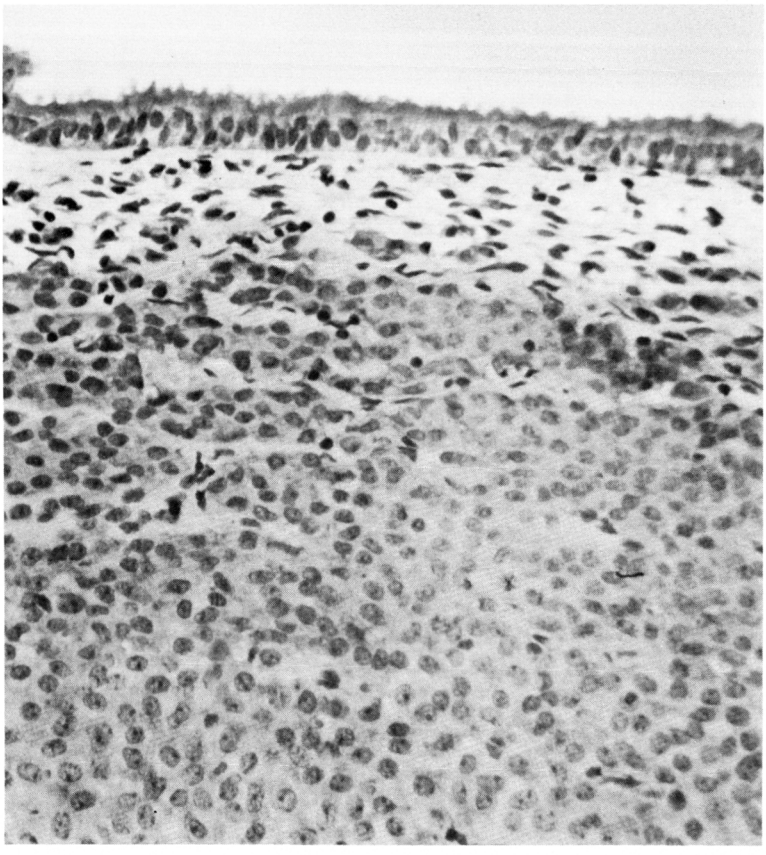

FIGURE 5. Growth hormone secreting chromophobe adenoma. The tumor has eroded the floor of the pituitary fossa; a thin rim of connective tissue separates the mass from sphenoid sinus epithelium (H&E × 160).

epithelium of the sphenoid sinus. This case illustrates the well-known invasive tendencies of histologically benign pituitary tumors. With H&E and special stains, the cytoplasm is definitely chromophobic.

In this instance, the pathologist and the clinician were faced with an anomaly: a chromophobe adenoma with high GH levels and the clinical features of incipient acromegaly. EM, however, demonstrated that the tumor cells contained large numbers of electron dense secretory granules (figure 6). The ultrastructural picture is similar to the previously discussed eosinophil adenoma but with some notable exceptions. First, the granules are not as numerous in this case, and the granules are smaller, averaging 120 mm in diameter.

Harvey Cushing was the first to observe that pituitary tumor in acromegalics were not necessarily eosinophilic but might show the same histology as chromophobe adenomas.[1] The advent of EM revealed that virtually all of these GH producing tumors contained cytoplasmic granules. Two size ranges have been reported: 300 to 500 mm diameter granules occur most commonly in typical eosinophil adenomas, whereas chromophobe or mixed tumors causing acromegaly contained smaller and fewer granules.[11,12] In either event, the hormone produced is the same, and the size difference is independent of the methods of fixation.

In figure 7 is illustrated the size distribution in two cases of acromegaly. The curve on the right represents the size distribution in the case described previously,

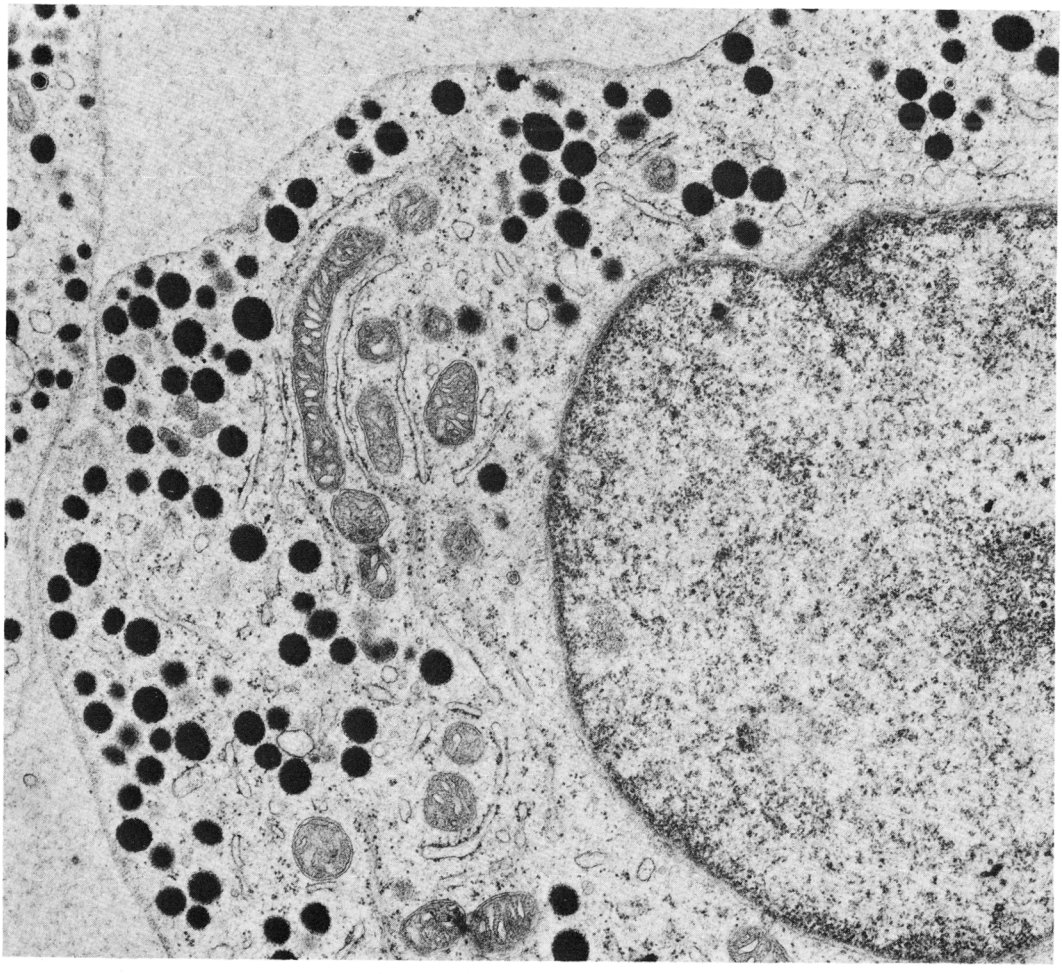

FIGURE 6. Growth hormone secreting chromophobe adenoma. The secreting granules are smaller and fewer than in the eosinophil adenoma in figure 4 (× 21,000).

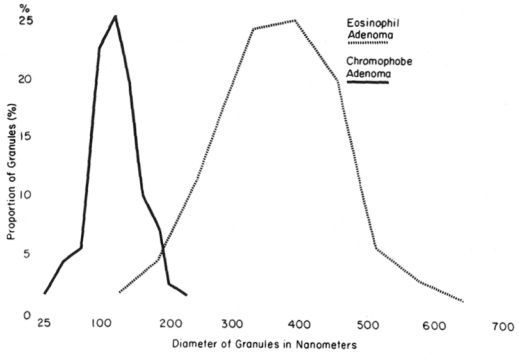

FIGURE 7. Comparison of secretory granule size in two GH secreting pituitary adenomas. The curve of the left from the chromophobe is typically narrower and steeper.

a typical eosinophil adenoma. The curve on the left is from the case under discussion, a chromophic tumor causing acromegaly. The proportion of granules is represented along the ordinate. Both are basically bell shaped, normal distributions. Typically, the chromophobe has a steeper curve with a narrower range.

Thus, GH producing tumors may appear chromophobic because the granule size and concentration is so small as to be invisible by ordinary light microscopic techniques. Many explanations have been advanced to account for this phenomenon. In some reports, the highest serum GH

levels are associated with tumors having the smallest and fewest granules. This inverse relationship between granularity and hormonal activity may simply reflect the timing of the surgical procedure and the phase of tumor activity. Therefore, the highly granulated tumors may be in "storage phase," while chromophobe tumors may be in an "exhaustion phase."[13] Another possibility is that the granules have no predetermined size: they simply grow until they are extruded.

In some adenomas they tend to enlarge and accumulate because of continuing, slower growth.[11] The latter possibility suggests an inverse relationship between granularity and the *rate* of hormone production. These speculations are supported by a high degree of correlation between morphologically defined "secretory indeces" and pre-operative serum GH levels.[20]

Malignant Pituitary Adenomas

Pituitary tumors are frequently so undifferentiated that they defy recognition and classification by light microscopy. It is in this area that EM is a particularly useful diagnostic tool, as illustrated by the following example. A 40-year-old woman had a two year course of asthenia, fatigue and vague headaches. An endocrine evaluation revealed mild panhypopituitarism. There were no significant general physical or neurological findings, but radiographic studies demonstrated a huge pituitary mass with erosion of bone and extension into the middle cranial fossa, sphenoid sinus and nasopharynx. Routine histology shows a malignant epithelial neoplasm with nuclear pleomorphism and numerous mitotic figures (figure 8). The cytoplasm is amphophilic and gives no reaction with special stains for secretory granules.

A conservative diagnosis of "poorly differentiated carcinoma" was rendered, but it was not possible to identify the lesion as definitely of pituitary origin. Electron photomicrographs of this tumor, however, show a very familiar picture (figure 9). The cytoplasm contains an admixture of organelles including mitochondria, rough endoplasmic reticulum and Golgi cisternae. In addition, there are several membrane bound secretory granules of the sort seen in most endocrine inactive pituitary chromophobe adenomas. They provide sufficient morphologic evidence to establish the diagnosis of an hypophyseal tumor and to enable the physicians to institute a plan of therapy.

This lesion raises the issue of what constitutes malignancy in a pituitary neoplasm. The medical literature indicates that it means different things to different people.[23] Clinicians in general and some pathologists call malignant any pituitary tumor which spreads beyond the confines of the sella turcica and invades neighboring structures such as the sphenoid sinus and cavernous sinus.[7] Other authors insist upon nuclear atypia, mitoses and distant metastases before using the term "pituitary carcinoma."[2] Some have suggested that the terms "malignant" and "carcinoma" be aban-

TABLE I

Electron Microscopic Findings in Pituitary Adenomas

Histopathology	*EM Features*
Endocrine inactive chromophobe adenoma	100 - 150 nm secretory granules arranged along plasma membrane of cell.
Eosinophil adenoma causing acromegaly	Densely packed, large granules filling cytoplasm, obscuring other organelles; broad size range averaging 375 nm.
Chromophobe adenoma causing acromegaly	Secretory granules smaller and fewer; average diameter 120 nm; narrow distribution curve.
Malignant adenoma	Scattered secretory granules identify pituitary origin of tumor cells.
Oncocytoma	Tumor cells filled with mitochrondria having branching christae and matrix inclusions.

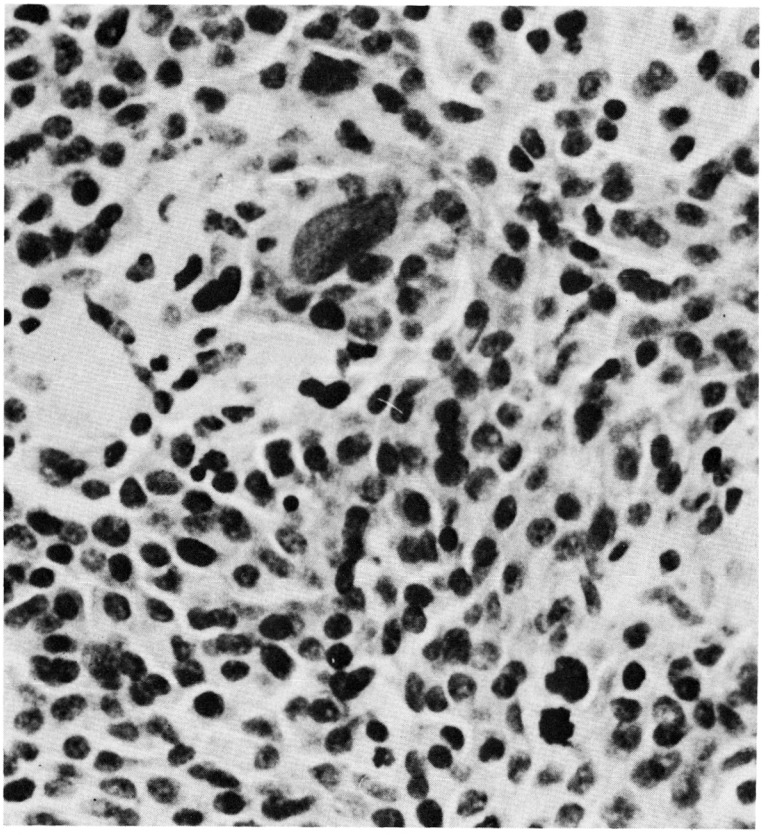

FIGURE 8. Malignant pituitary adenoma. There is nuclear pleomorphism and scattered mitoses (H&E × 250).

doned altogether, substituting "invasive" or "aggressive" in their stead.[14] Regardless of this semantic controversy, it should be recognized that the natural history of pituitary tumors is often unpredictable, and that they commonly destroy surrounding structures, infiltrate brain and disseminate throughout the subarachnoid space.

Pituitary Oncocytoma

Another example of the usefulness of EM is in the diagnosis of the rare oncocytoma of the pituitary gland. An opportunity was available to examine a lesion of this nature in a 47-year-old woman who had severe headaches, amenorrhea and subarachnoid hemorrhage two years previously. Later, she developed personality change, weight loss and a bloody discharge from her nose and mouth. Physical examination revealed loss of pubic and axillary hair and a bitemporal hemianopsia. Serum GH levels and urinary steroids were depressed.

Computerized axial tomography demonstrated a soft tissue mass extending into the cavity of the sphenoid sinus, expanding the pituitary fossa, and reaching into the region of the third ventricle. Routine histology in figure 10 shows cells in a diffuse pattern with abundant pink cytoplasm. The nuclei are vesicular, hyperchromatic and pleomorphic. Dark pigment granules were noted in several fields. Because of the pink cytoplasm, the diagnosis of an eosinophil adenoma was entertained, but not supported, by special stains for secretory granules. Other diagnostic considerations, including granular cell tumor, melanoma and malignant astrocytoma, were excluded by a variety of special stains for lipofuscin, melanin and glial fibrils.

At last EM demonstrates densely packed abnormal mitochondria often with branched tubular christae, filling the cytoplasm of tumor cells (figure 11). Electron dense inclusions are present in the mitochondrial matrix.

This tumor meets the light microscopic and EM criteria for the diagnosis of an oncocytoma, i.e., its composition by cells with plump, eosinophilic granular cytoplasm almost completely filled with mitochondria. Oncocytes are normally present in several organs including the thyroid, parathyroid and salivary glands. Tumors of oncocytes, both benign and malignant, are known to occur in these and other organs. Oncocytes were once believed to comprise a distinct system of cells but are not thought to be derived from preexisting parenchymal cells by some degenerative processes, perhaps the result of cellular senescence or the manifestation of some obscure mitochondrial disorder.[5]

Oncocytes in human pituitary gland were first described in 1970 by Paiz and Hennigar who examined serial sections by light microscopy and EM. Oncocytic tumors of the pituitary gland were not recognized until fairly recently.[9,10] Scattered case reports appeared in the literature until 1975 when a systematic EM study of

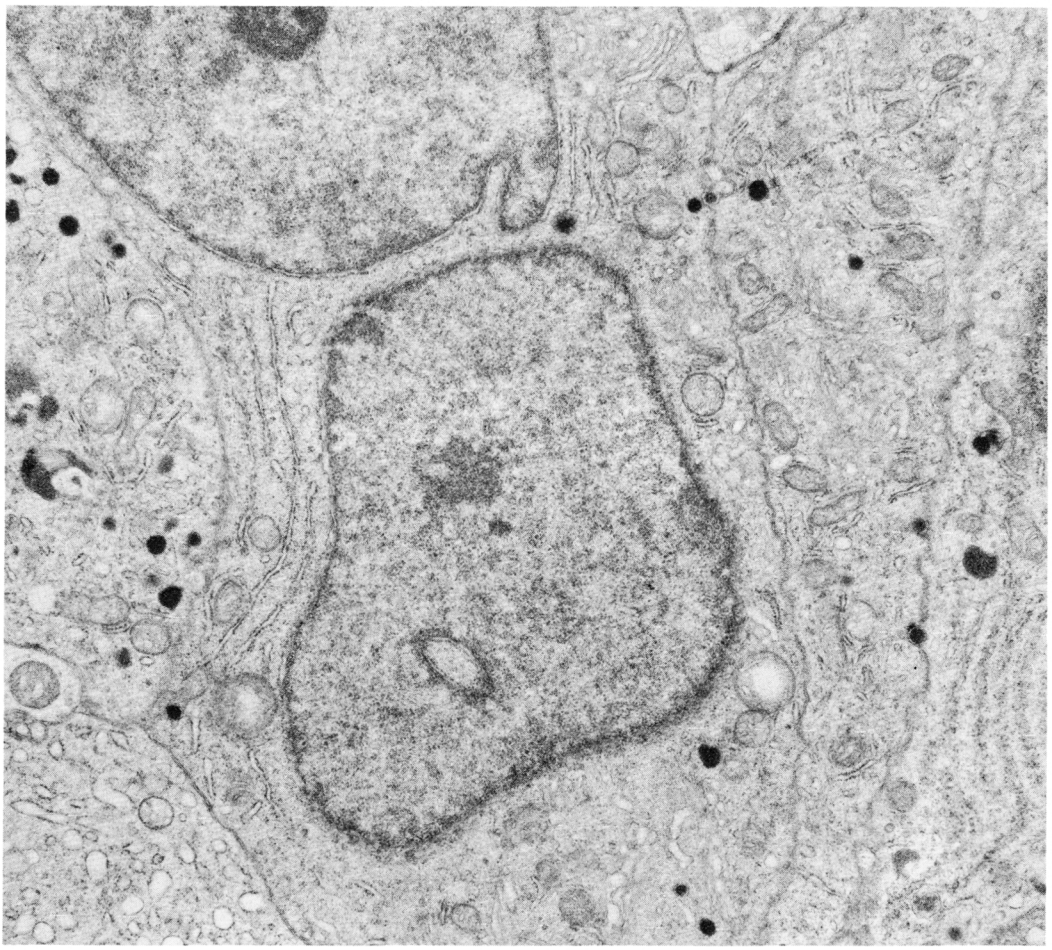

FIGURE 9. Malignant pituitary adenoma. The small secretory granules identify the pituitary origin of the neoplasm (× 12,000).

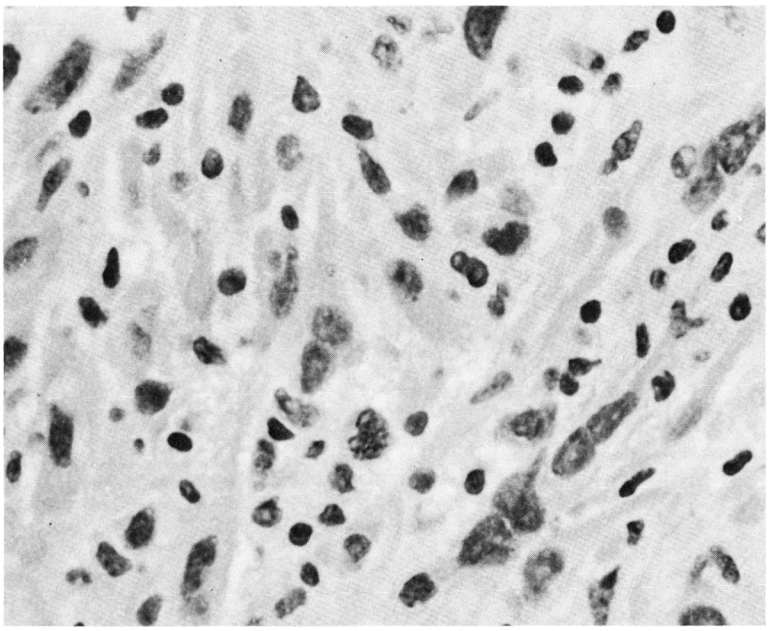

FIGURE 10. Pituitary oncocytoma. The cytoplasm is eosinophilic and finely granular. Nuclei are bizarre and pleomorphic (H&E × 250).

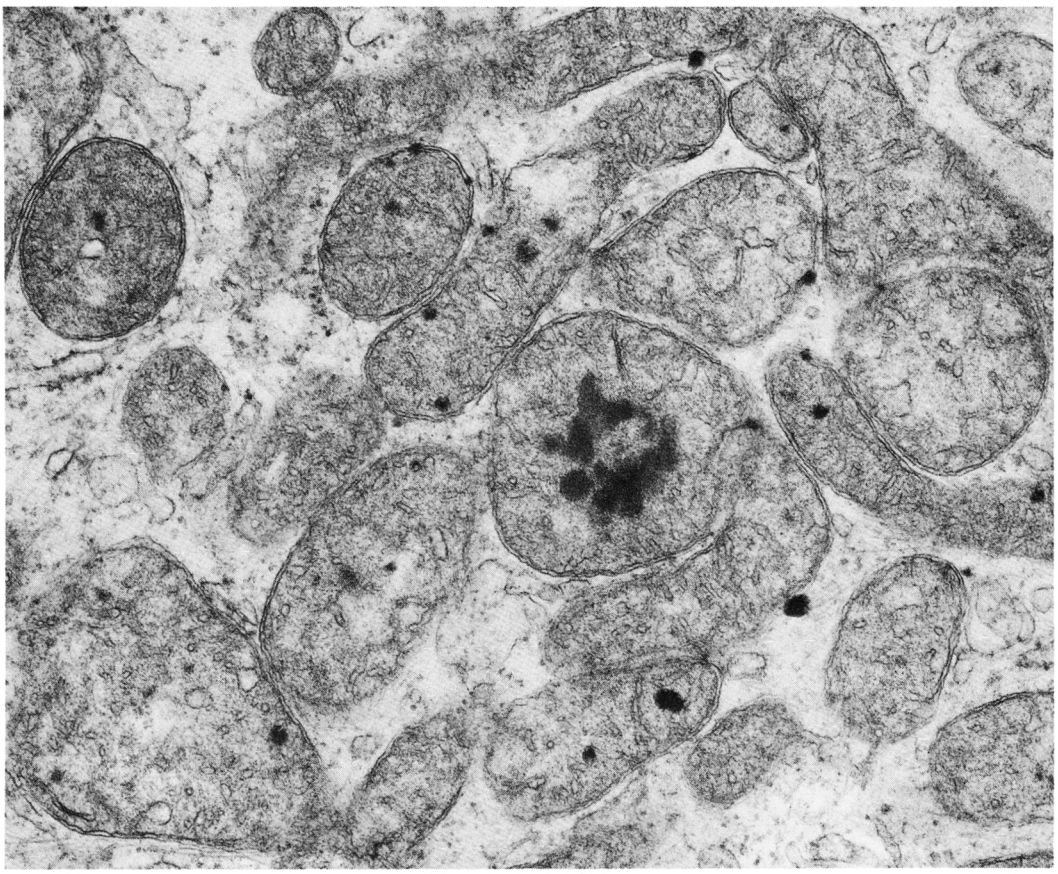

FIGURE 11. Pituitary oncocytoma. Cells are filled with abnormal mitochondria having branched and tubular christae and electron dense inclusions (× 33,000).

a large series of pituitary tumors indicated that the incidence might be as high as 16 percent of all pituitary neoplasm.[21] It now appears that many pituitary oncocytomas have been misdiagnosed as chromophobe or eosinophil adenomas. It is evident from this example that the diagnosis and identification of these neoplasms require EM techniques.

Summary

The usefulness and limitations of EM in pituitary tumor diagnosis have been reviewed and illustrated with clinical examples. The light microscopic classification of chromophobe, eosinophil and basophil adenoma is often inconsistent with the hormonal activity of the tumor. Virtually all pituitary tumors contain some secretory granules, even those with no demonstrable hormonal activity. Chromophobe adenomas associated with acromegaly contain GH granules of abnormal size and concentration. Because tumor cells may produce abnormal size granules, the identification of tumor cell type of hormone by granule measurement alone is not reliable. Undifferentiated neoplasms may defy classification by light microscopy. Ultra-structural studies can identify the pituitary origin of these lesions by the demonstration of secretory granules. The definitive diagnosis of pituitary oncocytomas requires EM, which will show large numbers of bizarre mitochondria distending the cytoplasm of tumor cells.

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