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Heterogeneous Pituitary Adenomas

A Light Microscopic, Immunohistochemical and Electron Microscopic Study

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Summary. The combined use of several histological procedures (i.e. conventional light microscopy, immunohistochemistry and electron microscopy) among 45 unselected pituitary adenomas demonstrated the existence of 9 tumors (20%) containing several identifiable adenohypophyseal cell types. The cellular associations were between 2 or 3 identifiable cell types. Mammosomatotrophic tumors were the most frequent but not the only mixed type (somatomammocorticotrophic, somatocorticotrophic tumors were also found). The cellular components varied in size but the cells appeared randomly distributed in the tumors. In all the adenomas there was an unidentified cell component (no reactivity with antisera used) varying from sparse to numerous elements. On adjacent sections the adenomatous cells reacted with a single specific antiserum, but in two cases the immunohistochemistry on contiguous paraffin embedded sections did not confirm this with certainty. These results confirm those of others and a new term is purposed to designate these tumors: heterogeneous pituitary adenomas. According to the nature and the proportions of the cell components the heterogeneous adenomas were subdivided into two groups: a group A which comprised adenomas formed by a major identifiable cellular type associated with one or two other less frequent cell types, and a group B formed by a predominant unidentifiable (no reactivity with immunochemical stainings) cell type associated with one or two other identified cell types. The present morphofunctional classifications of pituitary adenomas should be modified to include homogeneous adenomas with a single cell type and heterogeneous adenomas with several cell types.

Key words: Human pituitary adenoma – Light and electron microscopy – Immunohistochemistry – Several adenohypophyseal cell types

Introduction

The application of electron microscopy and immunohistochemistry to pituitary adenomas allows the identification of adenohypophyseal cell types they contain.

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Some pituitary tumors with several hypophyseal cell types were described in large series of pituitary adenomas, but they were considered to be special cases and underwent no further study (Peillon et al. 1970; Halmi and Duello 1976; Horvath and Kovacs 1976; Girod et al. 1976; Saeger 1977; Solcia et al. 1977; Shimizu et al. 1978; Ezrin et al. 1979; Duello and Halmi 1980; Kovacs et al. 1980; Martinez et al. 1980; Trouillas et al. 1980). Other papers individualized particular pituitary adenomas showing an association of various adenohypophyseal cell types, especially the mixed growth hormone-prolactin cell tumors (Linquette et al. 1969; Guyda et al. 1973; Zimmerman et al. 1974; Corenblum et al. 1976; Horn et al. 1976; Cunningham and Huckins 1977; Duello and Halmi 1977; Horvath et al. 1977; Brun et al. 1979; Favre et al. 1979; Scanarini and Mingrino 1979).

The present work combined the use of light microscopy, immunohistochemistry and electron microscopy. We investigated a series of 45 unselected pituitary adenomas to demonstrate the existence of several adenohypophyseal cell types.

Material and Methods

We studied 45 pituitary adenomas removed either transsphenoidally or by transfrontal neurosurgery. For *light microscopy*, pieces of all the tumor tissues were fixed in Bouin's or Bouin-Hollande's fluid and embedded in paraffin. Sections were serially cut (3–4 μm) and stained with conventional techniques: haematoxylin-eosin, Herlant's tetrachrome, PAS-Orange G procedure, Alcian blue and aldehyde thionin-PAS Orange G.

For *immunohistochemistry*, the indirect immunofluorescence, the indirect immunoperoxidase and the Sternberger's peroxidase anti peroxidase (PAP) methods were applied on serial sections of each tumor, with different antisera: anti h GH, anti o-Prl, anti h Prl, anti 1–39 and 1–24 h ACTH, anti o LH_α, anti o βLH, anti oβFSH, and anti b βTSH. The primary antiserum was reacted with the tissue at different dilutions (1:100 to 1:250) for 3 h at room temperature or 12 h at +4° C. For immunofluorescence, the immunological reaction was visualized by using anti rabbit immunoglobulin sheep gamma globulins conjugated with fluorescein isothiocyanate (Institut Pasteur, Paris). For the immunoenzymatic reaction, after the primary incubation with specific antiserum, the slides were incubated with peroxidase labelled sheep antibody anti rabbit (Institut Pasteur, Paris) or with horseradish peroxidase anti horseradish peroxidase complex (Cappel Laboratories). The peroxidase was revealed by 3-3′ diamino-benzidine or 4 chloro-l-naphtol. All the washings and dilutions were performed in 0.05 M PBS (pH 7.2).

The specificity of immunostaining was verified by several controls: omission of one step; substitution of normal serum or PBS for the specific primary antiserum; immunostaining with the same primary antibodies, of non tumorous pituitary gland or homologous pituitary adenomas (i.e.: reaction of the anti GH serum on a pituitary adenoma of a patient with acromegaly). Immunological reactions on adjacent sections were also performed.

For *electron microscopy*, small pieces (1 mm^3) of 15 tumors were fixed in 2.5% glutaraldehyde, post fixed in 2% osmium tetroxide in Sörensen's buffer, dehydrated in graded ethanol followed by propylene oxide and embedded in Epon-Araldite. Semithin sections (1 μm) were cut and stained with Toluidine blue. Nickel sections were cut from selected areas, stained with uranyl acetate and lead citrate, and viewed in an Hitachi 300 electron microscope.

Results

The combined use of light microscopy, immunohistochemistry and electron microscopy identifies 9 tumors composed of several adenohypophyseal cell types among 45 unselected pituitary adenomas.

Table 1. Clinical and endocrinological features. S. = somatotrophic; P. = prolactinic; C. = corticotrophic; T. = thyrotrophic; G. = gonadotrophic; n = normal level; ↑ and ↑↑ = increased and greatly increased level; ↘ = decreased level

Patient	Sex	Age (years)	Duration of symptoms (years)	Endocrine functions					Radiological tumor grade[a]	Clinical manifestations
				S.	P.	C.	T.	G.		
1.	F	31	?	/	/	/	/	/	II	Acromegaly
2.	F	50	?	/	/	/	/	/	II	Visual disturbances
3.	F	46	2	↑	↑	n	n	/	II	Acromegaly
4.	M	29	6	↑↑	↑	↑	n	n	III	Acromegaly
5.	F	48	1	↘	↑	/	n	↘	IIa	Visual disturbances
6.	M	58	6–7	↑↑	n	n	n	↘	III	Acromegaly
7.	F	25	2	/	↑↑	n	n	↘	III	Amenorrhoea-galactorrhoea
8.	F	65	?	/	↑	n	↑	↘	IIIb	Hypopituitarism
9.	M	24	4	↑	n	↘	n	n	III	Acromegaly

[a] According to Hardy and Vezina 1976

Clinical Findings

The 9 adenomas were removed surgically from 6 women and 3 men for 24 to 65 years old. The clinical and endocrine features are summarized in Table 1: 5 patients suffered from acromegaly, 1 from amenorrhoea-galactorrhoea, 1 from hypopituitarism and 2 from visual disturbances.

Macroscopic Findings

The tumors were well delimited but varied in size (from 3 to 15 mm), colour (whitish or grayish), consistency (firm or soft) and structure (solid or cystic). Secondary changes as haemorrhage and necrosis were particularly frequent and calcification was found in some cases. Thus, the gross anatomy did not contribute their differentiation from other pituitary adenomas.

Light Microscopic Findings (Table 2)

All the tumors examined are found to be adenomas: the cellular proliferation appears monomorphous with an architectural pattern of diffuse type or sinusoidal type. Some pseudo-rosettes around blood-vessels are present. Abundant vascularization takes the form of blood-vessels with a normal thin wall or, more often, with a thick hyalinized wall. Some tumors are pseudoencapsulated by compressed pituitary tissue with a little fibrosis.

By conventional stains the pituitary adenomas are divided into two groups:

– in 6 tumors, (cases n° 1, 2, 3, 4, 5 and 8) the greater part of cells exhibit no staining in their cytoplasm. However in 3 cases (n° 3, 4 and 5) a few cells, dispersed between unstained elements, show orangeophilic granulations and

Table 2. Histological and immunohistological results. $++++$ = very numerous positive cells; $+++$ = numerous positive cells; $++$ = few positive cells; $+$ = sparse positive cells; $-$ = negative cells

Patient No.	Conventional staining				Immunostaining				Results	
	Hematoxylin eosin	Herlant's tetrachrome	PAS	Alcian blue	GH	Prl.	ACTH	LH_t	Identified cells	Unidentified cells
1.	eosin +	−	some cells +	−	+++	−	+	−	+++	++
2.	−	−	some cells +	−	+++	+	+	−	+++	++
3.	eosin +	orange G +	−	−	++++	++	−	−	++++	+
4.	eosin ++	orange G ++	−	−	+++	++	−	−	+++	++
5.	eosin +	orange G +	sparse cells +	−	++	++	+	−	+	++++
6.	eosin +++	orange G ++ erythrosin ++	−	−	++++	++	−	−	++++	+
7.	eosin +++	orange G + erythrosin +++	some cells +	−	+	++++	+	−	++++	+
8.	eosin +++	−	−	−	−	+	−	+	+	++++
9.	eosin ++++	orange G ++ erythrosin +	−	−	+++	+	++	−	++++	+

in 3 other cases (n° 1, 2 and 5) some large polygonal cells show strong PAS positivity in their cytoplasm.

– in 3 tumors (cases n° 6, 7 and 9) the greater part of the cells show intense staining. They are acidophilic with haematoxylin-eosin; with Herlant's tetrachrome numerous orangeophilic elements mingled with few erythrosinophilic elements are found in 2 cases (n° 6 and 9), and in one case (n° 7) numerous erythrosinophilic cells are mingled with a few orangeophilic cells and a few cells positive with PAS. In all 3 tumors of this group some cells without staining of their cytoplasm are always present.

Immunocytologic Findings (Table 2)

The adenomas are divided according to the number of the cells and their reactions to the different antisera.

– In 3 adenomas (obs. n° 3, 6 and 9) almost all the cells react with the anti h GH serum. There is also a second, rare type of cell connected with these predominant somatotroph cells formed of sparse elements which react with the anti h Prl. serum. In one case (obs. n° 9) there are also corticotroph cells.

– In one adenoma (obs. n° 7) the majority of the adenomatous cells react with the anti h Prl. serum. Between the mammotroph elements there are two others rare types of cells; one reacts with the anti h GH serum, and the other formed of large polygonal cells reacts with the anti ACTH serum. In these 4 tumors (obs. n° 3, 6, 7 and 9) some cells do not react with any of the antisera used.

– In 3 tumors (obs. n° 1, 2 and 4) fewer cells than in the four preceding adenomas react with the anti h GH serum. On the other hand one or two other identifiable cell types are found consisting of a few sparse elements: corticotroph (obs. n° 1 and 2) and mammotroph (obs. n° 2 and 4) cells. A fair number of cells do not react with any antiserum.

– In 2 tumors (obs. n° 5 and 8) the majority of cells do not react with any antiserum and constitute a large unidentifiable cell group. However, intermingled with these cells some rare elements are reactive: somatotroph, mammotroph and corticotroph cells in case n° 5, mammotroph and gonadotroph (βFSH) cells in case n° 8.

On adjacent sections, in 7 out 9 cases, the cells only appear to react with a single specific antiserum (Figs. 1 and 2). But in two cases (obs. n° 6 and 9) the same cells seem to react with two antisera: anti h GH and anti h Prl.

Electron Microscopic Findings

Four tumors were studied by electron microscopy.

– In 2 cases (obs. n° 6 and 9) the cells are rounded or elongated, closely juxtaposed but without any junctional system. The nucleus is regular or slightly indented with fine evenly distributed chromatin. The cells contain many secretory granules, distributed throughout the cytoplasm or along the cell membrane, but no exocytosis is visible. These granules are rounded electron dense and

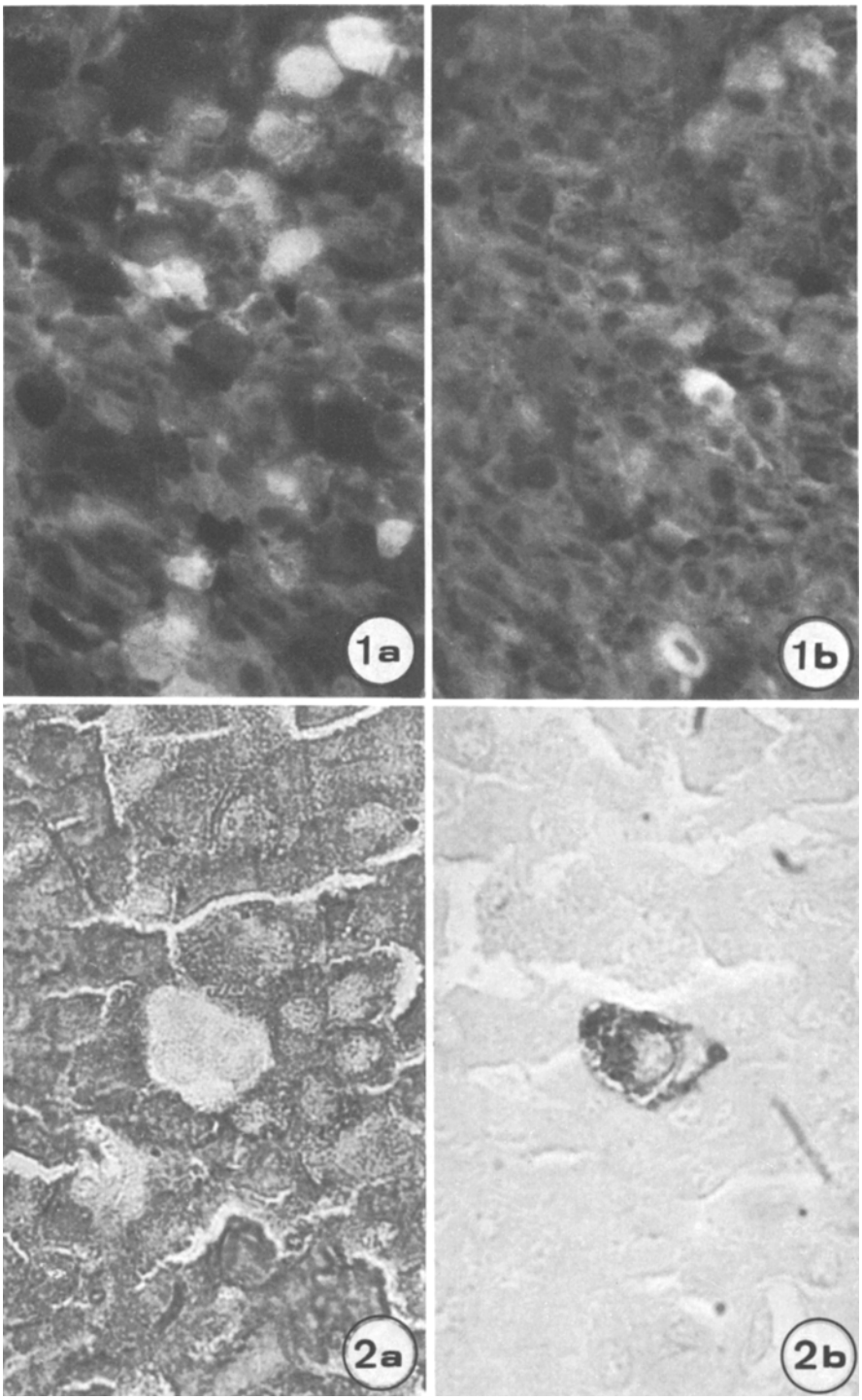
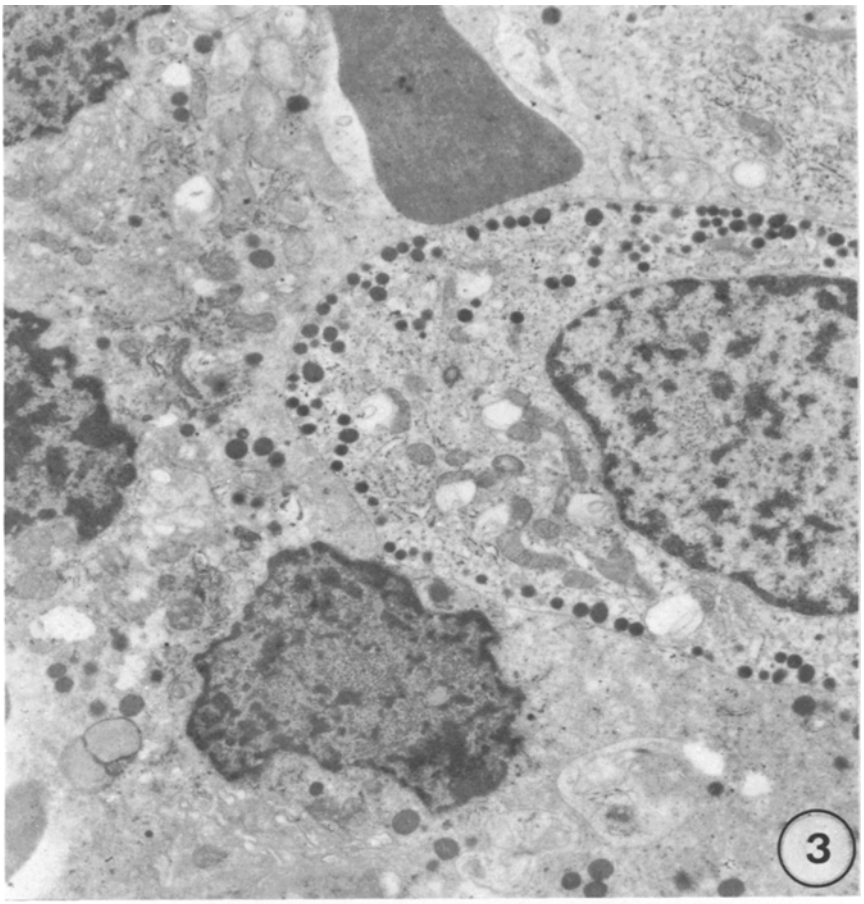


Fig. 1. Adjacent sections immunostained for growth hormone (**a**) and prolactin (**b**) showing the dissimilar distribution of the reactive cells. × 560

Fig. 2. a Intense immunostaining with an h GH antiserum of adenomatous cells, with the exception of one binucleated cell. **b** Contiguous section immunostained for prolactin showing intense reactivity only in the binucleated cell. × 710



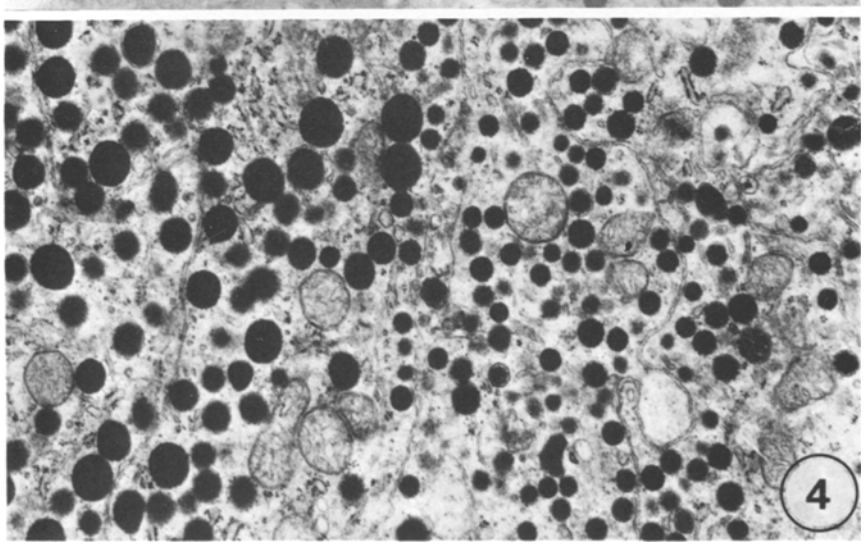


Fig. 3. Electron micrograph showing a different granular cell type among a poorly grar adenoma. $\times 10{,}000$

Fig. 4. Electron micrograph showing adjacent cells with secretory granules of different size. $\times$

homogeneous. Their size varies from 210 to 450 nm. Some of them occasionally appear up to 700 nm. Fibrous bodies composed of microfilaments, enclosing mitochondria, vesicles and some secretory granules are found in some cells. The Golgi apparatus is well developed and some lysosomes are found in the cytoplasm. In all the fragments examined only one aspect of cells is observed, the description of which corresponds with the somatotroph cells described in the acromegaly.

– In case 7 the majority of the cells consists of rounded or elongated elements juxtaposed with no visible junctional systems. The nucleus is often very irregular and indented. The cytoplasm contains few unevenly distributed secretory granules. They are electron dense, homogeneous but of varied size: irregular, curved. Their diameter varies from 220 to 760 nm. No exocytosis is observed. The mitochondria are rare and often altered. Numerous large vesicles are found. Mixed with these cells, the morphology of which resembles that of the mammotroph, there are two other types of cell (Figs 3 and 4). One is formed of small ovoid cells with a regular nucleus and cytoplasm containing many secretory granules with a diameter varying from 160 to 300 nm. These granules are randomly distributed along the cell membrane; no exocytosis is observed. The other cell type comprises large polygonal cells with an irregular excentered nucleus and a cytoplasm containing numerous secretory granules. These granules appear randomly distributed in the hyaloplasm, of varying electron density and with a slightly indented shape; their diameter varies from 220 to 450 nm. The description of these two cell types resembles that of the somatotroph and corticotroph cells respectively.

– In case 8 all the cells are similar in aspect. They are rounded and have an emphatic round nucleus with slight identations. In the cytoplasm there are few secretory granules: small (from 80 to 220 nm) regular, round with a varying electron density. The numerous mitochondria sometimes appear swollen with a dense matrix. There are several vesicles and lysosomes. These cells bear no morphological resemblance to any adenohypophyseal functional type; they correspond to unidentified nononcocytic cells.

Discussion

In our series of 45 unselected pituitary adenomas we observe 9 tumors with several identifiable adenohypophyseal cell types. These adenomas constitute an important group (20% in our series) which can be described as heterogeneous pituitary adenomas. The cell types vary in size and are sometimes sparse but they are diffusely distributed in the tumors. Girod et al. (1980) consider sparse immunoreactive elements to be normal included pituitary cells (they note: "according to their morphological data their scarcity, their localization often at the adenoma periphery,..., these cells seem to be normal included cells"), but in our opinion and according to Martinez et al. (1980), Cravioto et al. (1981) these elements must be considered to be adenomatous cells. In our cases they do not possess any distinctive morphological features to differentiate them from their neoplastic neighbors by light or electron microscopy, nor by immuno-

Table 3. Main studies of heterogeneous pituitary adenomas. S. = somatotroph cell; M. = mammotroph cell; C. = corticotroph cell; T. = thyrotroph cell; G. = gonadotroph cell

Authors	Year	Number of cases investigated	Number of heterogeneous adenomas	Cell types					Frequency of heterogeneous adenomas (%)
				S.	M.	C.	T.	G.	
Linquette M. et al.	1969	1	1	+			+		
Guyda H. et al.	1973	1	1	+	+				
Zimmerman E. et al.	1974	21	5	+	+				23.5
Corenblum B. et al.	1976	6	6	+	+				
Halmi N. et al.	1976	28	5	+	+				21.5
			1	+	+	+			
Horn K. et al.	1976	1	1		+		+		
Halmi N. et al.	1977	1	1		+		+		
Cunningham E. et al.	1977	1	1		+			+	
Heitz P.	1979	66	18	+	+	±	±	±	63.5
			18	+		±	±	±	
			4		+	±	±	±	
			2			±	±	±	
Martinez A. et al.	1980	50	25	+	+				56
			3	+		+			
Ilse G. et al.	1980	312	35	+	+				11
Girod C. et al.	1980	278	19	+	+				26.5
			55	±	±	±		±	
Total		766	201						26

histochemistry, and they appear randomly distributed in the tumor fragments. All the tumors containing several identifiable adenohypophyseal cell types must therefore be regarded as heterogeneous pituitary adenomas.

In various studies of pituitary tumors (Table 3) adenomas with several cellular components represent from 11 to 63.5% with an average of 26% (201 cases out of 766). The variation of frequency can be explained by the size of the series, the variety of the adenomas studied (grouped or not according to their clinical features) and the techniques used to identify adenohypophyseal cells.

In our series the varied cellular associations concern two (5 cases) or three (4 cases) identifiable cell types. There are two somato-mammotrophic adenomas, two somato-mammo-corticotrophic adenomas, one somato-corticotrophic adenoma and two tumors consisting for the most part of non reactive cells. These show, in one case, several somatotroph, mammotroph and corticotroph cells, and the other, several mammotroph and gonadotroph cells. The coexistence of somatotroph and mammotroph cells, with or without other cellular types is clearly predominant: in 7 adenomas out of 9 (79%). These results coincide with other findings (Girod et al. 1976 and 1980; Ezrin et al. 1979; Martinez et al. 1980). The cellular associations are made from 2 or 3 types of cells (except in one study: Heitz 1979). Somatomammotrophic tumors occur frequently (50%

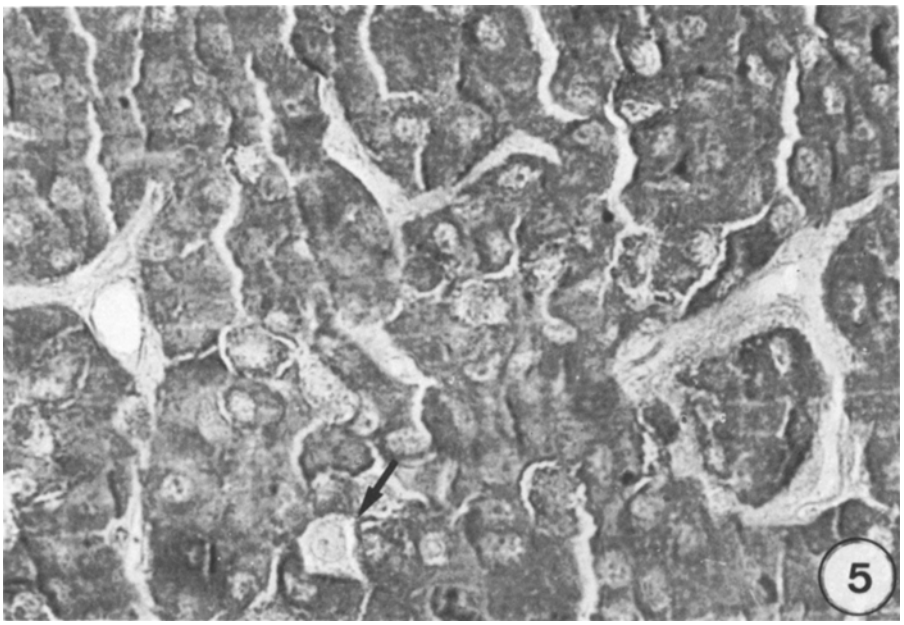


Fig. 5. Unidentified cell (*arrow*) among intense reactivity of an adenoma immunostained for growth hormone. ×710

of the heterogeneous adenomas) as do tumors including somatotroph and mammotroph cells connected with another cell type. The coexistence of somatotroph and mammotroph cells is found in 71% of heterogeneous adenomas. Other varied associations have been described (Demura et al. 1976; Cunningham and Huckins 1977; Duello and Halmi 1977; Müller et al. 1978; Favre et al. 1979). In every case there is an unidentified cell component (Fig. 5) which in 2 out of 9 cases of our series form the majority of adenomatous tissue. Electron microscopy (case n° 8) shows poorly granulated cells. These cells cannot be identified by immunohistochemical staining because of their insufficient or abnormal secretion which does not correspond with known or researched hormones on the pituitary level. Many studies have concentrated on the so called "chromophobe adenomas" which appear not to react in immunohistochemistry (Schechter 1973; Landolt 1975; Kovacs et al. 1976; Roy 1977). However some of these adenomas contain a few varied reactive cells: their frequency is low (7% for Girod 1980, 3% for Kovacs 1980, and 4.5% in our series). Seeing they contain several identified cellular types these adenomas may be connected to the heterogeneous pituitary tumors.

On adjacent sections 7 out of 9 of the adenomas in our series are composed of several reacting cell types, each with a single specific antiserum (Figs. 1 and 2). However in two cases the immunohistochemistry in light microscopy on contiguous sections does not clarify whether or not the same adenomatous cells react with two antisera (anti GH and anti Prl.). The majority of studies of heterogeneous adenomas using immunohistochemistry on adjacent sections

Table 4. Classification of pituitary adenomas

Homogeneous pituitary adenomas I	
	1. Growth hormone cell adenoma
	2. Prolactin cell adenoma
	3. Cortico-lipotroph cell adenoma
	4. Thyrotroph cell adenoma
	5. Gonadotroph cell adenoma
	6. Undifferentiated cell adenoma
	7. Oncocytic cell adenoma
Heterogeneous pituitary adenomas II	
Group A with predominant	1. Growth hormone cells
	2. Prolactin cells
	3. Cortico-lipotroph cells
	4. Thyrotroph cells
	5. Gonadotroph cells
Group B with predominant	6. Undifferentiated cells
	7. Oncocytic cells

(Zimmerman et al. 1974; Corenblum et al. 1976; Duello and Halmi 1980) show no double reaction on the same cells, except in three series (Horvath et al. 1977; Shimizu et al. 1978; Girod et al. 1980) where cells secreting the two hormones GH and Prolactin were found. These results have not been confirmed by ultrastructural immunocytochemistry on ultrathin adjacent sections. In animals the normal and tumoral adenohypophyseal cells can secrete several hormones (Ueda et al. 1973). In humans a plurihormonal secretion has been considered for the gonadotroph cells (FSH and LH; Phifer et al. 1973; Pelletier et al. 1976) and for corticotroph cells (ACTH, βLPH; Pelletier et al. 1977), but not for the other hormone producing cells.

The comparative study of the immunocytochemistry and the plasma levels of hormones show that an unfrequent cell type can be found at the heart of some adenomas while the corresponding hormone plasma level is normal (3 cases of our series) or decreased (2 cases of our series) and thus unsuspected on the clinical study. The heterogeneous adenomas are not necessary clinically multihormonal.

From these results the heterogeneous pituitary adenomas can be divided into two groups according to the nature and the proportion of cellular elements:

– group A (7 out of 9 in our series) are adenomas formed by one predominant cellular type which is granular and identified, associated with one or two small cellular components. The hormones secreted are identical or very similar to normal and these tumors are accompanied by a clinical and/or biological endocrine syndrome.

– group B (2 out of 9 in our study) the adenomas formed by a predominant non reactive cellular type which is unidentified and associated with one or two other identified cellular components composed of scattered elements. In general these tumors do not show up the endocrine level.

This work shows the reality and the importance of heterogeneous pituitary adenomas; the present morphofunctional classifications of pituitary adenomas (Saeger 1977; Landolt 1978; Ezrin et al. 1979) must be enlarged (Table 4) and must take tumors with several cellular types into account. Pituitary tumors can now be divided into homogeneous adenomas with a single cell type, identified or not, and into heterogeneous adenomas with several cell types. Several combined histological methods must be used to recognize these heterogeneous adenomas which are rarely suspected by the clinical and hormonal effects. Numerous points still need to be clarified, especially the origin of the adenomatous cells (stem cell, cell transformation) and whether they can secrete one or several hormones. Even more precise techniques are necessary, specially ultrastructural immunocytochemistry, which we are in the process of practising on the heterogeneous adenomas in our series.

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References

Brun JM, Bloch B, Bugnon C, Putelat R (1979) Grossesse gemellaire après bromocriptine chez une acromégale restée stérile après exérèse d'un adénome hypophysaire. Ann Endocrinol 40:551–552

Corenblum B, Sirek AMT, Horvath E, Kovacs K, Ezrin C (1976) Human mixed somatotrophic and lactotrophic pituitary adenomas. J Clin Endocrinol Metab 42:857–863

Cravioto H, Fukaya T, Zimmerman EA, Kleinberg DL, Flamm ES (1981) Immunohistochemical and electron-microscopic studies of functional and non functional pituitary adenomas including one TSH secreting tumor in a thyrotoxic patient. Acta Neuropathol (Berl) 53:281–292

Cunningham GR, Huckins C (1977) An FSH and prolactin secreting pituitary tumor: pituitary dynamics and testicular histology. J Clin Endocrinol Metab 44:248–253

Demura R, Kubo O, Demura H, Shizume K (1977) FSH and LH secreting pituitary adenoma. J Clin Endocrinol Metab 45:653–657

Duello TM, Halmi NS (1977) Pituitary adenoma producing thyrotropin and prolactin. Virchows Arch [Pathol Anat] 376:255–265

Duello TM, Halmi NS (1980) Immunocytochemistry of prolactin-producing human pituitary adenomas. Am J Anat 158:463–469

Ezrin C, Horvath E, Kovacs K (1979) Anatomy and cytology of the normal and abnormal pituitary gland. In: De Groot LJ, Cahill JF, Odell W, Martini L, Potts JT, Nelson Don H, Steinberger E, Winegrad AI. (eds): Endocrinology Vol I. Grune and Stratton, New York pp 103–121

Favre L, Rogers LM, Cobb CA, Rabin D (1979) Gigantism associated with a pituitary tumor secreting growth hormone and prolactin and cured by transsphenoidal hypophysectomy. Acta Endocrinol 91:193–200

Girod C, Dubois MP, Trouillas J (1976) Apport de l'immunofluorescence à l'étude cytologique des adénomas hypophysaires humains. Ann Endocrinol 37:279–280

Girod C, Mazzuca M, Trouillas J, Tramu G, Lhéritier M, Beauvillain JC, Claustrat B, Dubois MP (1980) Light microscopy, fine structure and immunohistochemistry studies of 278 pituitary adenomes. In: Derome PJ, Jedynak CP, Peillon F (eds) II European Workshop on pituitary adenomas, Asclepios Publ Ed, Paris, pp 3–18

Guyda H, Robert F, Colle E, Hardy J (1973) Histologic, ultrastructural and hormonal characterization of a pituitary tumor secreting both hGH and prolactin. J Clin Endocrinol Metab 36:531–547

Halmi NS, Duello TM (1976) "acidophilic" pituitary tumors. Arch Pathol Lab Med 100:346–351

Hardy J, Vezina JL (1976) Transsphenoidal neurosurgery of intracranial neoplasm. Adv Neurol 15:261–274

Heitz PU (1979) Multihormonal pituitary adenomas. Horm Res 10:1–13
Horn K, Erhardt F, Pickardt CR, Werder K, Scriba PC (1976) Recurent goiter, hyperthyroidism, galactorrhea due to a thyrotropin and prolactin producing pituitary tumor. J Clin Endocrinol Metab 43:137–143
Horvath E, Kovacs K (1976) Ultrastructural classification of pituitary adenomas. Can J Neurol Sci 3:9–21
Horvath E, Kovacs K, Singer W, Ezrin C, Kerenyi NA (1977) Acidophil stem cell adenoma of the human pituitary. Arch Pathol Lab Med 101:594–599
Ilse G, Ryan N, Kovacs K, Ilse D (1980) Calcium deposition in human pituitary adenomas studied by histology, electron microscopy, electron diffraction and X ray spectrometry. Exp Pathol Bd 18, 377–376
Kovacs K, Corenblum B, Sirek AM, Penz G, Ezrin C (1976) Localization of prolactin in chromophobe pituitary adenomas: study of human necropsy material by immunoperoxidase technique. J Clin Pathol 29:250–258
Kovacs K, Horvath E, Ryan N, Ezrin C (1980) Null cell adenoma of the human pituitary. Virchows Arch [Pathol Anat] 387:165–174
Landolt AM (1975) Ultrastructure of the human sella tumors. Acta Neurochir [Suppl] 22:1–167
Landolt AM (1978) Praktische Bedeutung neuer Erkenntnisse über Struktur und Funktion von Hypophysenadenomen. Schweiz Med Wochenschr 108:1521–1535
Linquette M, Herlant M, Fossati P, May JP, Decoulx M, Fourlinnie JC (1969) Adénome hypophysaire à cellules thyréotropes avec hyperthyroïdie. Ann Endocrinol 30:731–740
Martinez AJ, Lee A, Moossy J, Maroon JC (1980) Pituitary adenomas: clinocopathological and immunohistochemical study. Ann Neurol 7:24–36
Müller OA, Fink R, Werder KV, Scriba PC (1978) Hypersecretion of ACTH, growth hormone and prolactin in a patient with pituitary adenoma. Acta Endocrinol 87 (suppl 215):4–5
Peillon F, Vila-Porcile E, Olivier L, Racadot J (1970) L'action des oestrogènes sur les adénomes hypophysaires chez l'homme. Ann Endocrinol 31:259–270
Pelletier G, Leclerc R, Labrie F (1976) Identification of gonadotropic cells in the human pituitary by immunoperoxydase technique. Mol Cell Endocrinol 6:123–138
Pelletier G, Leclerc R, Labrie F, Cote J, Chretien M, Lis M (1977) Immunohistochemical localization of β lipotrophic hormone in the pituitary gland. Endocrinology 100:770–776
Phifer R, Midgley AR, Spicer SS (1973) Immunohistologic and histologic evidence that follicle-stimulating hormone and luteinizing hormone are present in the same cell type in the human pars distalis. J Clin Endocrinol Metab 36:125–141
Roy S (1977) Ultrastructure of chromophobe adenoma of the human pituitary gland. J Pathol 122:219–223
Saeger W (1977) Die Hypophysentumoren. In: Büngeler W, Eder M, Lennert K, Peters G, Sandritter W, Seifert G. (eds). Veröffentlichungen aus der Pathologie Vol 107. G Fischer, Stuttgart-New-York pp 1–240
Scanarini M, Mingrino S (1979) Pituitary adenomas secreting more than two hormones. Acta Neuropathol 48:67–72
Schechter J (1973) Electron microscopic studies of the human pituitary tumors. I- chromophobic adenomas. Am J Anat 158:371–386
Shimizu T, Ishida Y, Takeda F (1978) Electron microscopy of the human pituitary adenomas. Correlation of the secretory granules with experimentally and clinically evaluated hormone synthesis function of the adenoma tissue. Neurol Med Chir 18:107–117
Solcia E, Capella C, Buffa R, Frigerio B, Fontana P, Usellini L (1977) Tumori dell' adenoipofisi: diagnosi morfologica e classificazione. Pathologica 69:333–346
Trouillas J, Girod C, Lhéritier M, Claustrat B, Dubois MP (1980) Morphological and biochemical relationships in 31 human pituitary adenomas with acromegaly. Virchows Arch [Pathol Anat] 389:127–142
Ueda G, Moy P, Furth J (1973) Multihormonal activities of normal and neoplastic pituitary cells as indicated by immunohistochemical staining. Int J Cancer 12:100–114
Zimmerman EA, Defendini R, Frantz AG (1974) Prolactin and growth hormone in patients with pituitary adenomas: a correlative study of hormone in tumor and plasma by immunoperoxydase technique and radioimmunoassay. J Clin Endocrinol Metab 38:577–585

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