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Original Articles

Morphological and Biochemical Relationships in 31 Human Pituitary Adenomas with Acromegaly

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Summary. In 22 pure GH cell adenomas and 9 mixed GH cell-prolactin cell adenomas with acromegaly, we compare the morphological and functional data (secretory activity and granular appearance) with GH levels (radioimmunoassays) in the blood and in the tumor. According to morphological criteria, the secretory activity is marked in 13 cases (Group I), mild in 9 cases (Group II), and weak in 9 others (Group III). The mean values of the plasma GH levels in the 3 groups (80 ng/ml ± 22; 26.5 ng/ml ± 2; and 16.89 ng/ml ± 2 respectively) are significantly different. In 17 densely granulated adenomas and 14 sparsely granulated adenomas, the plasma GH values were very variable. The mean levels of these 2 groups (49.76 ng/ml ± 22 and 41.8 ng/ml ± 7.8 respectively) are not significantly different. The GH concentrations in the tumor were also very variable (358 to 78,900 ng/mg). Their highly significant relationship with the granular appearance is an indirect proof of the granular localisation of GH. We distinguish between 4 functional aspects of the GH cell adenoma which define the different levels of synthesis, storage, and excretion. The secretory activity of the GH adenomatous cell varies with the adenomas and differs from that of the normal cell.

Key words: Human pituitary adenoma – Acromegaly – Light and electron microscopy – Immunofluorescence – Radioimmunoassay of GH.

Introduction

The combined use of modern methods in the study of pituitary cytology (for detailed description see Girod 1976) allows precise cytological diagnosis of pure growth hormone (GH) cell adenoma or mixed growth hormone cell-prolactin cell adenoma in acromegaly. General morphological descriptions have been

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presented recently and are well documented (for reviews see Robert 1973; Landolt and Hosbach 1974; Bergland 1975; Olivier et al. 1975; Racadot et al. 1975; Saeger 1975; Halmi and Duello 1976; Horvath and Kovacs 1976; Nieuwenhuyzen Kruseman et al. 1976; Doniach 1977; Saeger 1977b; Solcia et al. 1977; Kinnman 1978; Landolt 1978a and b; Ezrin et al. 1979; Farmer 1979; Kovacs and Horvath 1979; Robert 1979; Girod et al. 1980). However, very little is known about the functional aspect of the GH adenoma cell. The object of the present report is to study this aspect by comparing the morphological and functional data shown by light microscopy, immunofluorescence, and electron microscopy with radioimmunoassays of GH levels in the blood and in the tumor.

Materials and Methods

We have studied 177 pituitary adenomas of which 67 were GH cell adenomas. Our study concerns 31 of them and 5 specimens of surrounding non tumourous anterior pituitary. These tumors were removed by trans-sphenoidal route from 31 acromegalic patients.

Tumor Grades

The size of tumor was approximated from lateral tomograms of the sella turcica and from pneumoencephalography. The tumor grade was noted according to Hardy and Vezina's macroscopic classification (Hardy and Vezina 1976):

Grade I: normal sella turcica: microadenoma.
Grade II: enlarged sella turcica: enclosed adenoma.
Grade III: enlarged sella turcica with erosion of the sellar floor.
Grade IV: "ghost" sella turcica: invasive adenoma.
According to this terminology, the suprasellar extension was expressed as follows:
0: no suprasellar extension.
a: slight imprint on the optochiasmatic cisterna.
b: complete amputation of the optochiasmatic cisterna.
c: upheaval of the floor of the III ventricle.

The tumors of our series were large (grade II: 18 cases; grade III: 13 cases). A suprasellar extension was present in 11 cases.

Histological Techniques

In each case, the adenoma samples obtained for morphological study were treated in the following way.

Light Microscopy. After fixation in Gérard's mixture (Bouin-Hollande-sublimate), the adenoma was embedded in paraplast; 4 micron sections were prepared and 4 or 5 adjacent sections were disposed on support-glass; they were stained with Herlant's tetrachrome, PAS-orange G, and thionine-paraldehyde-PAS-orange G.

Immunofluorescence (I.F.). Adjacent sections contiguous to the stained sections were treated according to the indirect reaction of Weller and Coons, with various antisera. The following antisera were used: anti-hGH, anti-oProlactin and anti-hProlactin, anti-α^{17-39} ACTH, anti-α and -βMSH, anti-βLH, anti-β and -γLPH, anti-α and βendorphins. Specificity controls were used (substitution of normal serum for the immune serum, absorption of the antibodies with an excess of the appropriate antigens); details of these procedures have been published (Girod 1977).

Electron Microscopy. Tissue fragments were fixed in 2% osmium tetroxide in 0.1 M cacodylate buffer, or in 2% glutaraldehyde in the same buffer; then they were post-fixed in 2% osmium tetroxide. They were embedded in Araldite. The ultrathin sections, cut in a Reichert OMU 3 ultramicrotome, were contrasted with uranyl acetate and lead citrate. They were examined with the JEOL type JEM 7 electron microscope.

Radioimmunological Assays

For all patients the mean basal value of plasma GH was established before surgery by radioimmunoassay. At least 3 samples were taken after an over-night fast ($N < 5$ ng/ml).

In 12 cases assays were carried out in the tumor. Each tumor was then cut into 3 pieces. The two intended for cytological study surrounded the central piece which was kept for the assays. This piece was immediately frozen and kept at $-70°$ C. After crushing the hormones were extracted by 3 successive buffers (phosphate buffer 0.05 M at pH 7.4 with saline 9 g/l; sodium bicarbonate 0.05 M at pH 10; ammonium sulfate 0.1 M at pH 4). After centrifugation, radioimmunoassays were carried out on each supernatant. The results were aggregated and expressed according to the wet weight of tumor. All the pituitary hormones were assayed, but only the GH values are mentioned in this study.

Statistics

For statistics, we used the Mann-Whitney test for comparing the mean values of GH. For the diagrams, we used the logarithm of the GH values.

The percentage estimate of the granular or immunostaining cells had only a comparative value since observation was carried out by the same person.

Results

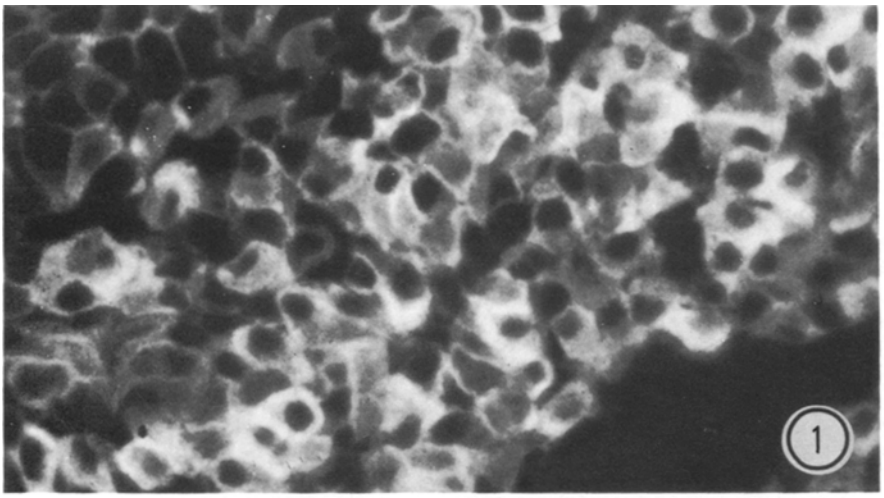
Our material is composed of 22 pure GH cell adenomas (S.) and 9 mixed GH cell-prolactin cell adenomas (S.P.).

Morphological and Functional Data

The study deals two essential characteristics of the GH adenoma cell: granular appearance and secretory activity.

1. The Granular Appearance. The *pure GH cell adenoma* is described as *densely granulated adenoma* (D.G. adenoma) when more than 50% of the cells show bright staining with orange G. In I.F., all the cells were strongly positive with hGH antiserum (Fig. 1) while the other antisera gave negative reactions. The ultrastructural examination confirmed the high granular density, which was much the same from cell to cell. The secretory granules were spherical or ovoid, and had an average size of 360 nm. They were distributed throughout the whole cytoplasm. In some cases, irregular extra-cellular electron dense deposits were found (Fig. 3).

In the *sparsely-granulated GH cell adenoma* (S.G. adenoma), the orangeophilic cells were scattered or non existent. In I.F., the proportion of cells which



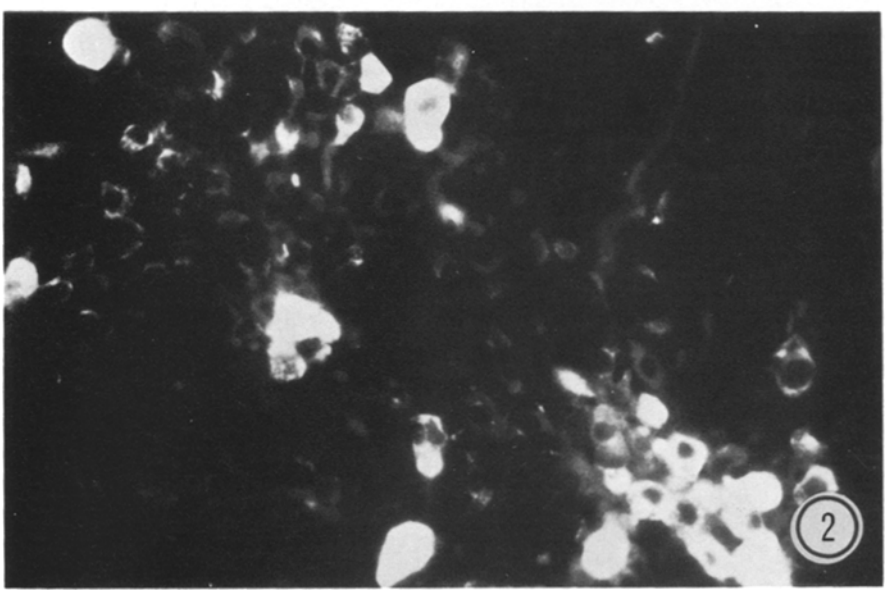


Fig. 1. Densely granulated GH cell adenoma. IF: all the cells were positive with an hGH antiserum. ×170

Fig. 2. Sparsely granulated GH cell adenoma. IF: areas of negative and positive cells with an hGH antiserum The phenomenon of functional variability is evident. ×150

reacted positively with hGH antiserum was much greater than that of the orangeophilic cells. It varied between 10 and 70% and was thus lower than in the densely granulated adenoma. There were areas of negative cells (Fig. 2). A phenomenon suggesting functional variation is evident: some large cells are strongly positive and other smaller ones are slightly stained. In one case there

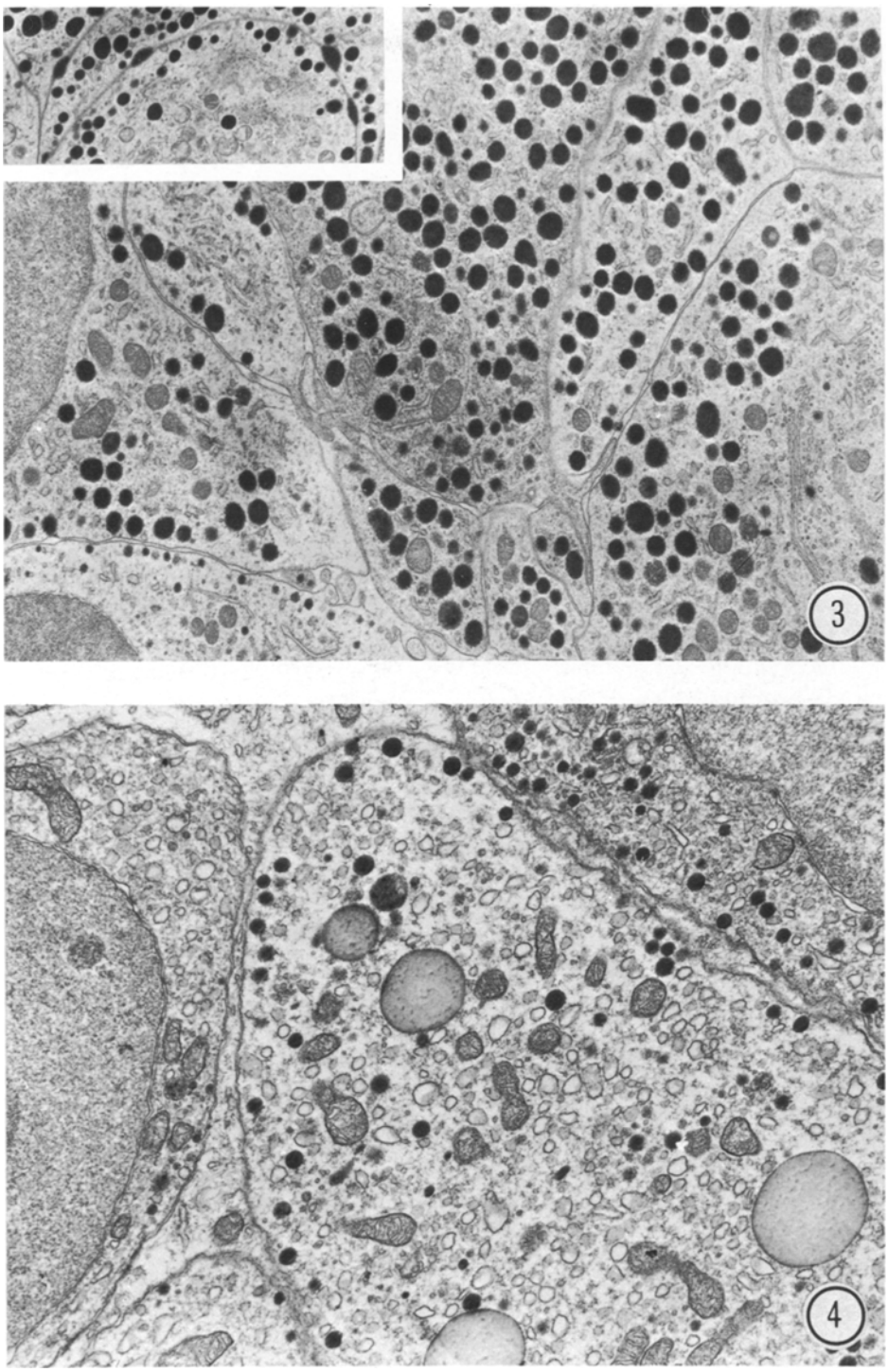


Fig. 3. Densely granulated GH cell adenoma with many secretory granules ($\times 4{,}500$), and irregular extracellular electron dense deposits (inset: $\times 4{,}500$)

Fig. 4. Sparsely granulated GH cell adenoma with few secretory granules, vesicular rough endoplasmic reticulum. $\times 10{,}500$

were only very rare positive cells. In electron microscopy, the number of granules (generally of small diameter: 150–250 nm) varied from cell to cell but was generally low (Fig. 4). In some cases, there were granule extrusions on the far side of the cells.

In brief, fibrous bodies composed of either microfilaments only or of endoplasmic reticulum, mitochondria, and some secretory granules were found more frequently in this variant; they were located on the concave side of the crescent-shaped nucleus (Fig. 6). These fibrous bodies have been previously mentioned by several authors (for reviews see Landolt 1975; Horvath and Kovacs 1978).

The *mixed GH cell – prolactin cell adenoma* was composed of two kinds of cells which were either densely or sparsely granulated. The two cell types, sometimes shown by Herlant's tetrachrome, are only clearly identified by I.F. Using I.F. on adjacent sections the cells immunoreacting with anti-hGH are different from those reacting with anti-oPRL and anti-hPRL. In one case (n° 3) some cells react with both anti-hGH and anti-hPRL antisera; we have never observed transitional forms. In 9 cases, the diagnosis of mixed adenoma was not established in spite of the occasional positive cells with anti-prolactin, anti-βLH or anti-α^{17-39} ACTH. We considered the proportion of these cells negligible in comparison with the great number of GH cells.

According to the granular appearance, the 31 adenomas can be separated into two groups:

- 17 densely granulated adenomas, 2 of which were mixed,
- 14 sparsely granulated adenomas, 7 of which were mixed.

2. Secretory Activity. By *light microscopy*, the degree of activity of the GH cells was evaluated by the size and the pleomorphism of the nuclei, by the existence of one or two large nucleoli, and, when the adenoma was densely granulated by the presence of a large Golgi complex (macula). By *electron microscopy*, in addition to the abovementioned criteria, we considered the extensive development of both a Golgi complex and of a rough endoplasmic reticulum (Fig. 5) to be indicative of activity. Nevertheless, a large quantity of lipid vacuoles seemed to be rather a sign of weak secretory activity (Figs. 4 and 6).

According to all of the criteria assembled in Tables 1 and 2, the 31 cases of our study were divided into 3 groups:

- Group I, marked secretory activity (+ + +): 13 cases,
- Group II, mild secretory activity (+ +): 9 cases,
- Group III, weak secretory activity (+): 9 cases.

Morphological Functional and Biochemical Relationships

1. Relationships Between the Tumor Grade, Plasma GH Levels and Secretory Activity (Fig. 7). The tumor grades were compared with the plasma GH levels and the secretory activity in each case. As the tumors of grade II and III without suprasellar extension were approximately the same size, they were gathered into the same group (A), with the largest tumors with suprasellar extension

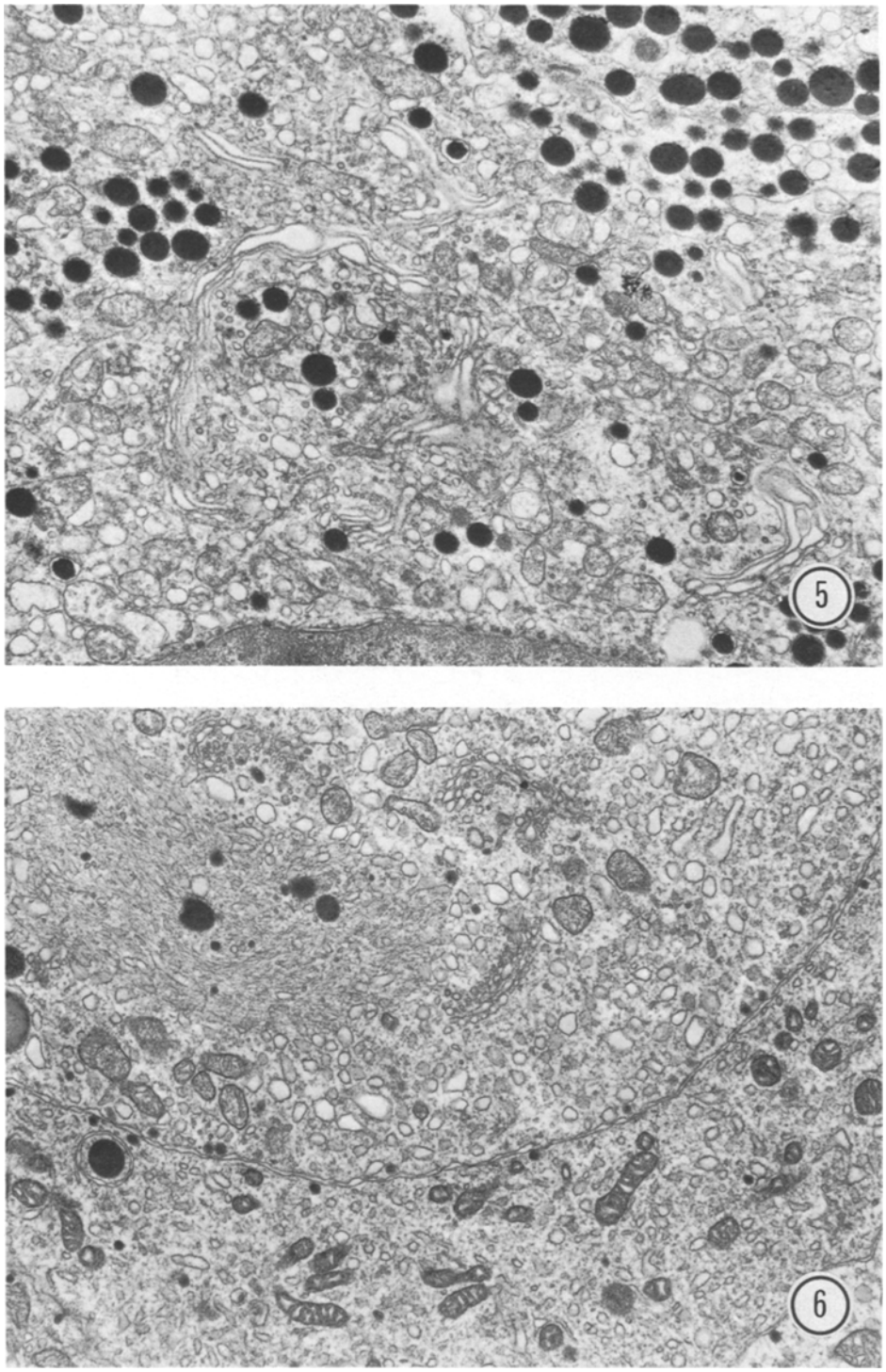


Fig. 5. Densely granulated GH cell adenoma with marked secretory activity showing a wide Golgi complex. ×13,750

Fig. 6. Sparsely granulated GH cell adenoma with weak secretory activity, and fibrous body in a small Golgi area. ×17,500

Table 1. Cytological characters of densely granulated adenomas. S = pure GH cell adenoma; S.P. = mixed adenoma; P = pleomorphic; R = regular; + to + + + = variations of size or of abundance of cytomembrane systems and granulations; Ex = Exocytosis; Fil = microfilaments; Gr = granulations.

Case number	Type	Light microscopy			Immunofluorescence		Electron microscopy				Degree of activity
		Nucleus size, form	Nucleolus size	Granular cells	Anti-hGH	Anti-PrL	Rough R.E.	Golgi complex	Gr.	Fil.	
1	S	+ + + P	+ + +	60%	100%	2 C.+	+	+ +	+ + +	+	+ +
2	S	+ + R	+	100%	100%	0	+	+	+ + +	0	+
3	S.P.	+ + R	+	60%	90%	80	+	+ +	+ +	+	+ +
4	S	+ + P	+ +	80%	80%	5 C.+	+	+ +	+ + +	+	+ +
5	S	+ + R	+ +	100%	100%	0	+ +	+ + +	+ + +	0	+ + +
6	S	+ + + R	+ + +	80%	100%	5 C.+	+ +	+ + +	+ +	0	+ + +
7	S.P.	+ + P	+ + +	70%	60%	40%	+	+ + +	+ + Ex.	+	+ + +
8	S	+ + + P	+ + +	70%	100%	0	+	+ + +	+ + +	0	+ + +
9	S	+ + R	+ +	60%	100%	0	+	+ +	+ + +	0	+ +
10	S	+ + R	+	50%	100%	0	+	+	+ + +	0	+
11	S	+ + P	+ + +	90%	> 99%	< 1%	+ +	+ + +	+ + + Ex.	0	+ + +
12	S	+ R	+	100%	+	0	+	+	+ + +	0	+
13	S	+ + P	+ + +	80%	100%	0	+ +	+ + +	+ +	+	+ + +
14	S	+ + R	+	90%	100%	0	+	+ +	+ + +	0	+ +
15	S	+ + + P	+ + +	90%	100%	2 C.+	+	+	+ + +	0	+
16	S	+ + R	+ +	100%	100%	0	0	+	+ +	+	+
17	S	+ R	+	90%	100%	0	+	+ +	+ + Ex.	0	+ +

forming another (B). The mean values of plasma GH in the 2 groups (35.05 ng/ml ± 3.46 and 70.46 ng/ml ± 34.25 respectively) were not significantly different, but in each group the tumors with a marked secretory activity had the highest GH plasma levels.

2. Relationships Between Secretory Activity and Plasma GH Levels (Fig.8). The morphological data were compared *a posteriori* with the mean basal values of GH in each case.

In group I (marked secretory activity), the GH values were the highest. In groups II and III they were medium or relatively low. The mean values of the 3 groups (80 ng/ml ± 22; 26.5 ng/ml ± 2 and 16.89 ng/ml ± 2 respectively) are significantly different taken in two ($T_{(2-1)} = 1.0$; $P << 0.001$. $T_{(3-2)} = 9.5$; $P < 0.05$).

3. Relationships Between the Granular Appearance, Plasma GH Levels and GH Concentrations in the Tumor (Fig. 9). In the D.G. and S.G. cell adenomas the plasma GH values were very variable. Whether or not an extreme value of 400 ng/ml was excluded, the mean levels of these 2 groups (49.76 ng/ml ± 22 and 41.8 ng/ml ± 7.8 respectively) were not significantly different.

Table 2. Cytological characters of sparsely granulated adenomas. S = pure GH cell adenoma; S.P. = mixed adenoma; P = pleomorphic; R = regular; + to + + + = variations of size or of abundance of cytomembrane systems and granulations; Ex = Exocytosis; Fil. = microfilaments; Gr. = granulations.

Case number	Type	Light microscopy			Immunofluorescence		Electron microscopy				Degree of activity
		Nucleus size, form	Nucleolus size	Granular cells	Anti-hGH	Anti-Prl	Rough R.E.	Golgi complex	Gr.	Fil.	
18	S	+ P	+ +	0	2 cel. +	0	+	+	+	+	+
19	S.P	+ R	+ +	0	40%	40%	+ +	+ + +	+	0	+ + +
20	S.P	+ P	+	0	20%	20%	+ +	+ + +	+ Ex.	0	+ + +
21	S.P	+ P	+	0	10%	< 1%	0	+	+	+ +	+
22	S	+ + + P	+ + +	< 1%	30%	0	+	+ + +	+	0	+ + +
23	S	+ + + R	+ + +	< 1%	70%	0	+	+ + +	+	0	+ + +
24	S	+ P	+	0	10%	1 C. +	+	+ +	+	+ +	+ +
25	S.P	+ + P	+ +	1%	40%	40%	+	+ + +	+	+ +	+ + +
26	S	+ + P	+ +	0	80%	0	+	+ +	+	0	+ +
27	S	+ R	+ +	0	10%	0	+	+	+	+	+
28	S.P	+ + R	+ +	0	30%	10%	+	+ + +	+ Ex.	0	+ + +
29	S.P	+ + R	+ +	< 1%	30%	2%	+	+	+	+ +	+
30	S	+ + R	+ +	0	10%	0	+	+ +	+	+ +	+ +
31	S.P	+ + R	+ + +	< 1%	30%	1%	+ + +	+ +	+	+	+ + +

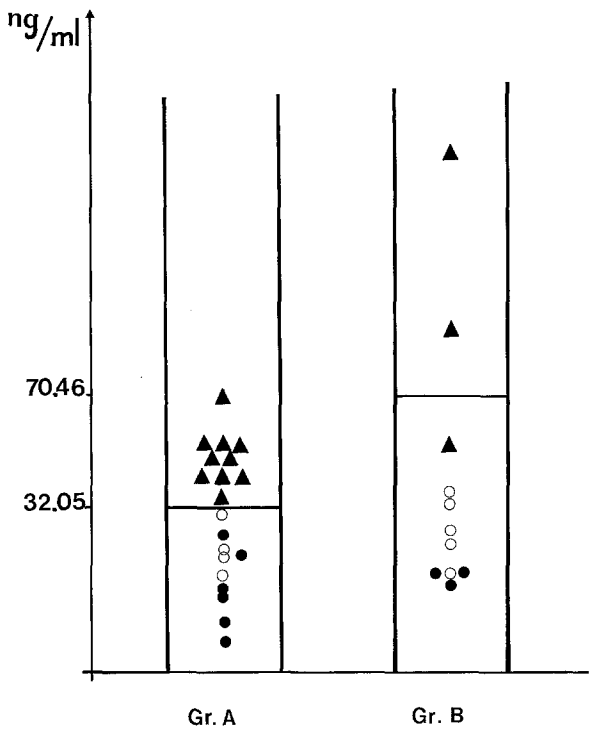
The 12 pieces in which assays were carried out comprised 7 D.G. and 5 S.G. cell adenomas. In the 7 D.G. adenomas the concentration of GH in the tumor was very high, varying from 8,650 ng/mg to 78,900 ng/mg with an average of 31,082 ng/mg ± 9,114 and a standard-deviation of 24,114. This value was twice the mean concentration of GH in a normal anterior pituitary (m = 16,610 ng/mg; extreme values: 10,000 and 33,000 ng/mg; n = 15). In the 5 S.G. cell adenomas, the concentrations of GH in the tumor were clearly lower (Fig. 9) between 358 and 3,247 ng/mg with a mean value of 1,746 ng/mg ± 563 and a standard deviation of 1,259. The mean concentration of GH in the S.G. cell adenomas represented 1/10th of the mean concentration in a normal anterior pituitary. The difference between the mean values of the 2 groups was highly significant (T = O; $P = 0.001$).

The morphological/functional and biochemical relationships enabled us to distinguish between 4 functional aspects of the GH cell adenoma (cf. Table 3):

– *densely granulated cell adenoma with marked or mild secretory activity:* every cell was positive with anti-hGH antiserum; the GH concentration in the tumor was very high and the basal plasma level was high;

– *densely granulated cell adenoma with weak secretory activity;* the GH concentration in the tumor was high but the GH plasma value was relatively low;

– *sparsely granulated cell adenoma with marked secretory activity or degranulated cell adenoma;* the proportion of positive cells with anti-hGH antiserum was



Gr. A : II_o : 20, II_o : 23, II_o : 40, III_o : 50, II_o : 35, II_o : 5, II_o : 40, II_o : 23, II_o : 45, II_o : 15, II_o : 16, II_o : 31, II_o : 9, III_o : 49, III_o : 45, III_o : 40, III_o : 70, III_o : 24, II_o : 50, III_o 26,

Gr. B : II_b : 18, III_a : 25, III_a : 400, II_a : 27, III_b : 33, III_b : 50, III_a : 20, II_b : 36, II_a : 20, II_b : 20, III_c : 126,

Fig. 7. Relationships between tumor grade, plasma GH levels and secretory activity. Gr. A: tumors of grade II_0 and III_0; Gr. B: tumors of grade II and III with suprasellar extension; plasma GH levels of tumors with marked secretory activity (▲), mild secretory activity (○), weak secretory activity (●)

less than in the densely granulated group; the GH concentration in the tumor was low but the GH plasma value was high;

– *sparsely granulated cell adenoma with weak secretory activity;* positive cells with anti-hGH antiserum were very rare; the GH values in the tumor and the plasma were relatively low.

Relationship Between the Adenoma and the Surrounding Non-Tumorous Anterior Pituitary

In the 5 pieces of surrounding non tumorous pituitary (cases n° 9, 15, 17, 26, 27) all cell-types were observed by light microscopy, particularly "normal" GH cells. In case n° 17, assays in the pituitary were carried out. The GH

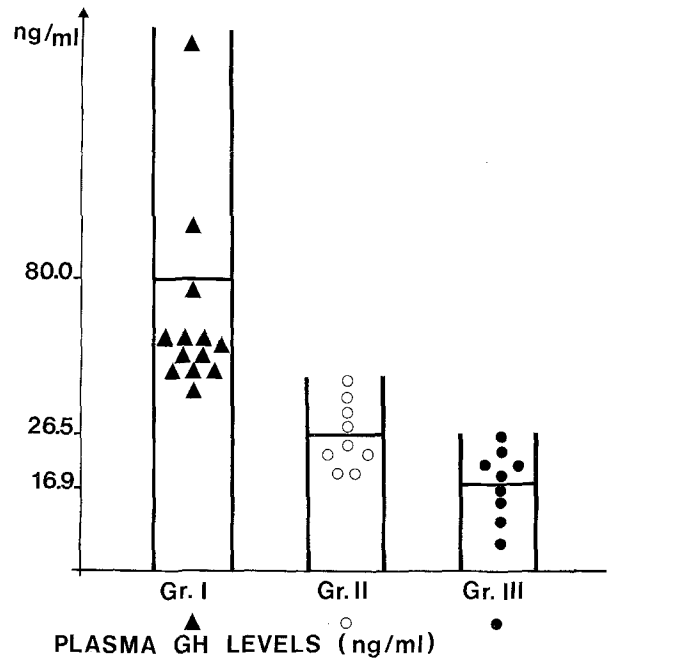
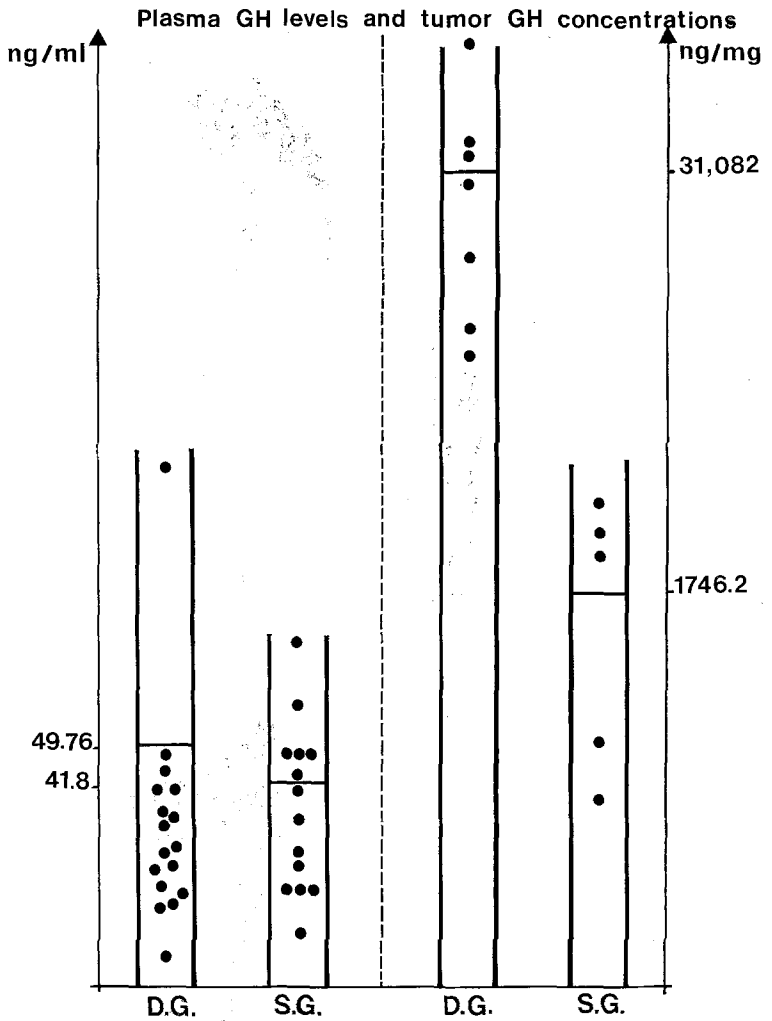


Fig. 8. Relationships between secretory activity and plasma GH levels. Gr. I (▲): marked secretory activity; Gr. II (○): mild secretory activity; Gr. III (●): weak secretory activity

Table 3. Functional aspects of the GH cell adenoma. S = pure GH cell adenoma; S.P. = mixed adenoma; S.A. = secretory activity; Gr. = granulations; D.G. = densely granulated adenoma; S.G. = sparsely granulated adenoma.

Case number	Cyto-logical Diagnosis	Morphology		GH		Morphofunctional diagnosis
		S.A.	Gr	Plasma ng/ml	Tumor ng/ml	
5	S	+++	D.G.	400	28,987	
11	S	+++	D.G.	40	11,473	Densely granulated cell adenoma
14	S	++	D.G.	33	78,904	with marked or mild secretory
17	S	++	D.G.	31	37,069	activity
1	S	++	D.G.	20	36,905	
16	S	+	D.G.	16	15,591	Densely granulated cell adenoma
15	S	+	D.G.	15	8,647	with weak secretory activity
19	S.P	+++	S.G.	49	3,247	Sparsely granulated cell adenoma
31	S	+++	S.G.	126	2,541	with marked secretory activity
29	S	+	S.G.	26	2,041	Sparsely granulated cell adenoma
21	S.P	+	S.G.	20	357.8	with weak secretory
18	S	+	S.G.	9	544.4	activity



Plasma GH levels (ng/ml)

D.G. 5 15 16 18 20 23 23 25 27 31 33 35 40 40 45 50 400

S.G. 9 20 20 20 24 26 36 40 45 49 50 50 70 126

Tumor GH concentrations (ng/mg)

D.G. 8,647 11,473 15,591 28,987 36,905 37,069 78,904

S.G. 357.8 544.4 2,041 2,541 3,247

Fig. 9. Relationships between granular appearance plasma GH levels on the left and tumor GH concentrations on the right. *D.G.* densely granulated adenoma; *S.G.* sparsely granulated adenoma

concentration was 3 times higher in the adenoma (37,069 ng/mg) than in the surrounding pituitary (10,136 ng/mg) where it was at the lower limit found in the normal anterior pituitary. The concentrations of other hormones were practically zero in the tumor but equivalent to those of a normal pituitary in the surrounding piece.

Discussion

Our material included more densely granulated than sparsely granulated adenomas. Their frequency (54.8%) is less than that found by Lewis and Von Noorden (80%) (1972) but comparable to that of Young et al. (1965). In the S.G. adenomas, the proportion of positive cells with anti-hGH antiserum ranges between 10 and 70% and is lower than in the D.S. adenomas. In a group of 8 cases, Zimmerman et al. (1974) found 5 cases with a "chromophobic aspect" (corresponding to S.G. adenoma); 7 react variably with anti-hGH immunserum (in 3 cases there are less than 30% of immunoreactive cells; in 3 cases the percentage is between 30–60%; in 1 case it is between 60–90%). Our series included 9 mixed GH cell-prolactin cell adenomas. This mixed adenoma, with immunoreactive GH and prolactin cells is not uncommon in acromegalic patients; some observations have been reported (Guyda et al. 1973; Zimmerman et al. 1974; Corenblum et al. 1976; Halmi and Duello 1976; Mashiter et al. 1979). Does the presence of two categories of secreting cells prove the existence of two independent lines of tumor cells, or is it a morphological index of the evolution of a common precursor, the so-called "acidophilic stem cell adenoma of the human pituitary" (Kovacs et al. 1977)? This question is not clearly resolved.

We have shown that there is a significant relationship between morphological signs of secretory activity and the mean basal values of plasma GH. Our results are comparable to Saeger's (1973a and b) who found the same relationship in 11 GH cell adenomas. We have found a discrepancy in 3 cases (n° 1, 15, 29) between the nuclear signs of cellular activity observed by light microscopy and the ultrastructural signs of a weak secretory activity, as did Saeger. We have given priority to these ultrastructural signs in order to establish the degree of secretory activity. Indeed we consider that pleomorphism of nuclei with an increased number of mitoses does not indicate secretory activity, but rather an increased rate of tumor growth.

In our 31 adenomas, the granular appearance of the GH cells was not significantly related to the plasma GH levels. Thus it seems that, contrary to the normal GH cell a poorly granulated appearance is not always associated with high GH secretion and vice versa. Therefore the degree of secretory activity of the tumor cannot be deduced from the granular appearance alone. For example in our material, the adenoma which had the highest plasma GH levels (400 ng/ml) was densely granulated with strong secretory activity. Of the 2 adenomas which had the lowest levels (5 and 9 ng/ml), one was densely granulated and the other sparsely granulated with weak secretory activity. These results are in contrast to those of Lewis and Van Noorden (1972) who, in a comparable study based on 78 cases, concluded that there was "an inverse correlation between granularity and secretory activity". These authors did not take account of a great range of GH levels (20 to 1,150 ng/ml), in their "poorly granulated" group, equivalent to our sparsely granulated group, which could falsify the comparison of means by a *t*-test. For us the granularity of the adenoma GH cell corresponds more to the degree of storage than to activity. The observation of Fanghanel-S et al. (1978) seems to be in agreement with this: the cells of pituitary tumors in acromegalic patients contain more granulation after bromocriptine treatment than do controls. Bromocriptine probably inhibits exocytosis,

but not synthesis. The high GH concentration in the tumor is also in agreement with this suggestion.

The GH concentrations in the tumor were very variable from 358 to 78,900 ng/mg. Their highly significant relationship with the degree of granulation seems to be an indirect proof that in adenomatous cells GH is essentially in the granulations. This has been shown by electron microscopy, using the immunoenzymatic technique (Landolt 1978; Landolt and Rothenbühler 1977–1978). Our results agree with those of Young et al. (1965) who established the same relationship in 50 cases by using a biological method to evaluate the GH activity in the tumor. Radioimmunological assays were carried out by Lloyd et al. (1969) in 3 GH cell adenomas 2 of which were S.G. adenomas. The GH concentrations in the tumor were comparable to ours (600 ng/mg; 4,300 ng/mg; 8,600 ng/mg). In our series including large tumors of grade II and III with or without suprasellar extension, a relationship with the tumor grade and the plasma GH levels was not found. Forrest et al. (1965) have previously suggested that sellar size and serum level of GH were not correlated. Wright et al. (1969) and Klijn et al. (1979) have found that the plasma GH level was moderately or very, well correlated with the maximum lateral sellar area. This discrepancy between the authors shows that it is difficult to evaluate the tumor size with precision, and that plasma GH levels are not correlated only with the size of tumor but also with other factors, such as the secretory activity.

In comparison with the GH secretion by the adenoma GH secretion by the surrounding non tumorous pituitary was negligible, but probably not zero. In fact, in 5 pieces we observed normally granulated GH cells and found in one of them a GH concentration identical to that of the normal anterior pituitary. In other words, the hypersecretion of GH by the adenoma does not inhibit the secretion of GH in the neighbouring hypophysis. In the para-adenomatous adenohypophysis, Saeger (1977a) found only 5 cases with a normal appearance of the GH cells in 15 cases of well-differentiated GH-cell adenoma.

We have found several functional aspects of the GH cell adenoma as assessed by morphology. These aspects illustrate in our opinion the different levels of synthesis, storage, and excretion of GH, and the different relationship in the rates of the three phenomena. It seems that the secretory activity of the GH adenomatous cell varies according to the functional activity of the adenomas and differs from that of the normal cell. Anatomical relationships will be established to see if these functional changes correspond with the growth aspect of the GH cell adenoma or with initially different aspects.

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