

# Pathological Diversity in Clinical Syndromes of Pituitary Hypersecretion: Its Significance in Evaluating their Surgical Treatment

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**ABSTRACT:** Thorough pathological examination disclosed considerable diversity of abnormal cell types and correspondingly different surgical correction rates among patients with apparently similar syndromes of pituitary hypersecretion. The surgical correction of acromegaly in patients with densely granulated growth hormone tumours was threefold that in patients whose tumours showed sparse granulation. Two non-prolactinoma tumour types associated with hyperprolactinemia have aggressive growth patterns; their special therapeutic management is discussed. Of 33 patients with Cushing's disease solitary adenomas were found in only 14, while six patients had proven corticotroph cell hyperplasia. Elective hypophysectomy should replace selective adenectomy in selected cases of Cushing's disease.

**RÉSUMÉ:** La diversité pathologique dans les syndromes cliniques d'hypersécrétion hypophysaire: son importance dans l'évaluation du traitement chirurgical L'examen pathologique complet chez des patients qui présentaient des syndromes d'hypersécrétion hypophysaire semblables a montré une grande diversité dans le type de cellules anormales observées et donc dans le résultat des opérations correctrices. Dans l'acromégalie, le taux de succès était trois fois plus élevé pour les tumeurs à hormone de croissance dont les granulations étaient denses que pour celles à granulations éparées. Deux tumeurs de type non-prolactinome, mais associées à une hyperprolactinémie, semblent présenter une croissance agressive. Nous en discutons le traitement spécial. Chez 33 patients avec maladie de Cushing nous avons trouvé des adénomes solitaires chez seulement 14 sujets; 6 autres avaient une hyperplasie des cellules corticotrophes prouvée. L'hypophysectomie élective devrait remplacer l'adénectomie sélective chez certains cas de maladie de Cushing.

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Hypersecretory pituitary syndromes fall into three main clinical categories. Table 1 illustrates the relative incidence of pituitary syndromes or pituitary cell types encountered at operation for intrasellar tumour in a recent analysis of our series at the Wellesley Hospital, which now numbers over 300 cases. As in most reported general series of comparable size,<sup>1</sup> the three main hypersecretory syndromes involving growth hormone (GH), prolactin (PRL) and adrenocorticotrophic hormone (ACTH) account for two-thirds (67.8%) of the cases. Respectively, 71 showed clinical signs of acromegaly (with gigantism in two cases); 89 presented with amenorrhea and/or galactorrhea (or male impotency) and infertility; 32 had Cushing's disease. The cases within each of these three sub-populations were ostensibly uniform in their clinical and biochemical manifestations. However, detailed pathological analysis of the surgical specimens has revealed that these groups are not in fact homogeneous popula-

tions when studied from an immunocytochemical or electron microscopic viewpoint.

## Growth Hormone Hypersecretion: Acromegaly

It is now clear that apparently similar cases of acromegaly may result from any one of at least 5 histological tumour types that are distinctly recognizable by immunocytochemical and electron microscopic (EM) studies. Table 2 outlines the relative incidence of cell types and their combinations in 64 acromegalic patients whose histological study in this manner was complete.

**Mammomatotroph tumours** The relatively rare mammomatotroph tumour is a monomorphous tumour whose cells elaborate and release both growth hormone and prolactin, although growth hormone secretion greatly predominates. There is a male preponderance of its incidence. Earlier described as a primarily morphologic entity without specific clinical features,

**Table 1: Intraseptal Tumours**

	No.	%
Acromegaly, Giantism	71	25.1
Prolactinoma	89	31.4
Cushing's Disease	32	11.3
Nelson's Syndrome	4	1.4
Acidophile Stem Cell	4	1.4
Gonadotroph	4	1.4
Silent Corticotroph	10	3.5
Null Cell, Oncocytoma	26	9.2
Unclassified	19	6.7
Craniopharyngioma	12	4.2
Arachnoid Cyst	7	2.5
Mucocoele	1	0.4
Secondary Carcinoma	4	1.4
	283	99.9

**Table 2: Growth Hormone Tumours**

	No.	%
<b>Acromegaly</b>		
Densely Granulated HGH Cell Adenoma	18	28.1
Sparsely Granulated HGH Cell Adenoma	16	25
Mammotroph Adenoma	8	12.5
Polyhormonal Adenoma	7	10.9
Mixed Adenoma HGH + PRL	14	21.9
<b>Giantism</b>		
Mammotroph Adenoma	1	1.6
	64	100

its occurrence appears to indicate the formation of a tumour cell line from an early stem cell in the "eosinophilic" series.<sup>2</sup>

**Growth Hormone Cell Adenomas** The majority (53.1%) of GH secreting adenomas are of two cell types, the densely granulated (DG) and sparsely granulated (SG) GH cell adenomas. (See Fig. 1(a) and (b)) In another study<sup>3</sup> of 46 patients treated for acromegaly by selective trans-sphenoidal removal of GH-secreting adenomas, we were interested in correlating the efficacy of surgical treatment with a number of factors, including tumour stage, preoperative blood levels of GH, previous treatment, and histologic cell type. Our clinical population was typical of that of several similar surgical series of comparable size.<sup>4,5</sup> There was a 2:1 ratio of males to females, and an average age of presentation of 43.6 years. The duration of signs and symptoms ranged from 6 months to 30 years, with an average of 9 years, indicating a typical delay in diagnosis and treatment in keeping, perhaps, with a persistent tendency to regard acromegaly as a benign chronic illness.

Biochemical correction rates correlated typically both with tumour stage and size (see table 3) and also to a predictable degree with preoperative growth hormone levels (fig. 2). The rate of biochemical correction was a competitive 93% for stage 1 and stage 2 enclosed tumours.<sup>6</sup>

Of particular interest however, was the correlation of pre- and post-operative GH levels with tumour cell type in 34 patients whose pathological specimens were sufficient to allow their complete characterization by EM and immunostaining methods. Table 4 displays three findings. Neither SG nor DG GH cell adenomas showed a greater tendency to produce excessively high blood levels of GH. GH levels above and below 40 µg/L. were evenly distributed between SG and DG tumour cell types responsible. Despite this, the rate of correction was 94.4% for DG GH adenomas compared to only 56.3% for SG GH cell

tumours. Otherwise stated, DG GH cell adenomas accounted for nearly three-quarters of all cases corrected. This finding is open to interpretation, but it may signify important quantitative differences in granule formation and release by the two cell types. To date, we have found no correlation between cell granulation type and clinical symptoms, tumour size, recurrence rate, or anomalous responsiveness of GH to thyroid releasing hormone, though these are factors that are still under study.

**Mixed Adenomas** Mixed adenomas are bimorphous tumours with two distinct cell types, each containing either GH or prolactin. Their incidence in this series was 21.9%. The relatively high success rate (9/11) of their biochemical correction in this series may be a reflection of their histological pattern; they are almost without exception constituted by DG GH adenoma cells and SG PRL adenoma cells. Fig. 3 illustrates the correction of both GH and PRL hypersecretion in 4 such patients.

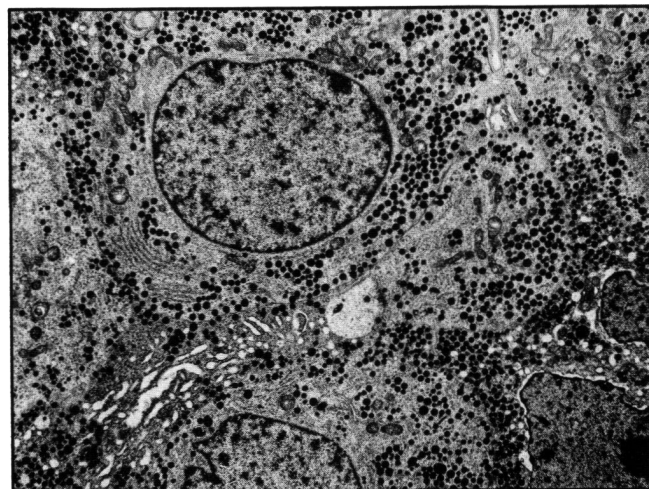
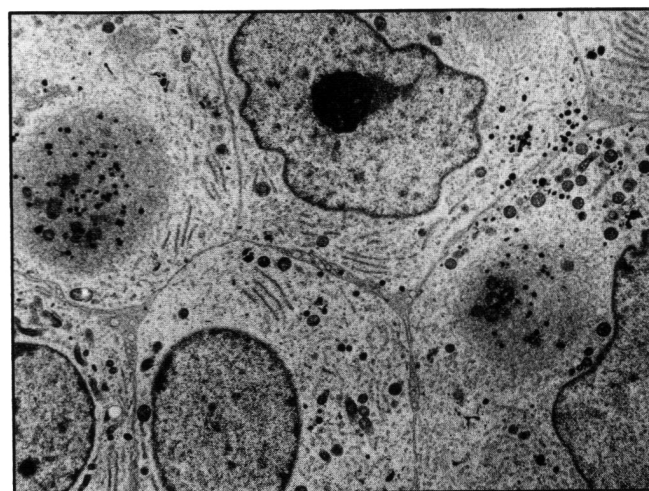


Figure 1(a) — Densely granulated GH cell adenoma. Electron micrograph (Mag. 11,200 X)



(b) — Sparsely granulated GH cell adenoma. Electron micrograph (Mag. 13,150 X)

Courtesy of Dr. E. Horvath and Dr. K. Kovacs, St. Michael's Hospital, Toronto

**Table 3: Surgical Correction — 46 Cases: Acromegaly**

Stage		No. Pts.	Corrected	%	
I		4	4	100	
	II	O	14	12	85.7
		A	6	6	100
B		3	3	100	
		27	25	92.6	
III	O	10	5	50	
	A	2	0	0	
	B	4	1	25	
IV	O	1	0	0	
	A	1	1	50	
	C	1	0	0	
		46	32	36.8	
		Overall		69.6%	

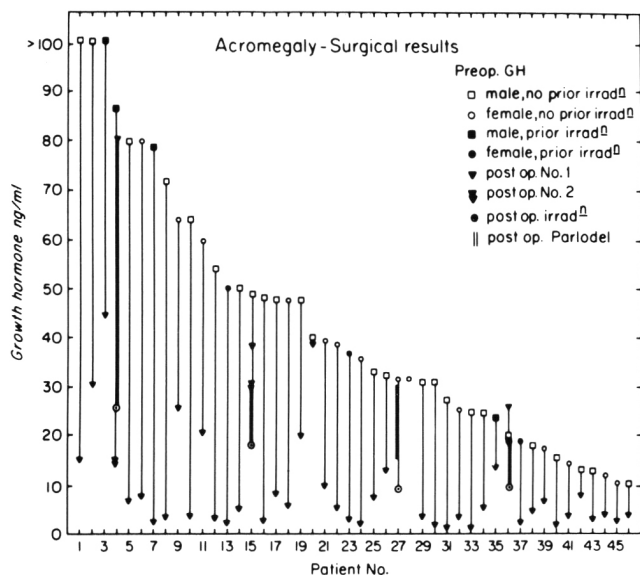


Figure 2 — Acromegaly: response to treatment - survey of 46 cases

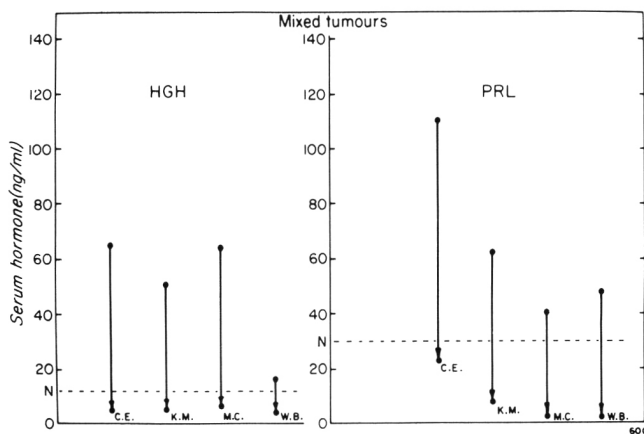


Figure 3 — Correction of both HGH and PRL levels in 4 patients with mixed adenomas.

**Table 4: Tumour Ultrastructure and Clinical Result: 34 Patients**

Tumour Type	GH Level (ng./ml.)			
	Pre-Operative		Post-Operative	
	>40 %	<40 %	>10 %	<10 %
Sparse Granulated GH Cell	6/13	46	10/21	48
Densely Granulated GH Cell	7/13	54	11/12	52
			1/18	6
			17/18	94

**Hyperprolactinemia**

A diversity of pathology was also found in patients with hyperprolactinemia. PRL is elevated non-specifically in a wide variety of physiological states, including sleep, exercise, stress, pregnancy and early lactation. Abnormal elevation of PRL may result from ingestion of phenothiazines, tricyclic antidepressants, beta-blockers, cimetidine and metoclopramide. When sustained hyperprolactinemia is associated with clinical or radiographic evidence of an intrasellar tumour, the differential diagnosis must include a variety of pituitary fossa lesions as well as prolactinoma. Table 5 illustrates the final histologic diagnosis in our first 60 cases of intrasellar tumour with hyperprolactinemia. Only 46 patients (76.6%) harboured true prolactinomas as confirmed by EM and immunocytochemical study.

Prolactin may be elevated in the presence of non-secreting tumours whose suprasellar extension interrupts the normal influence of the hypothalamic prolactin inhibiting factor — the so-called “stalk section” effect. Two other tumour cell types require specific mention.

**Acidophile Stem Cell Adenomas** The histologically immature and clinically aggressive acidophile stem cell adenoma is responsible for a clinicopathologic entity characterized by a short clinical history, local (particularly inferior) invasiveness, and relatively modest hyperprolactinemia. Although GH is also demonstrable in small amounts in a majority of these tumours, acromegalic features are rare, and females predominate.<sup>8</sup> In view of the invasive nature of their tumours, 3 of our 4 cases have received postoperative radiation, and it is now our policy to recommend this for all such patients, even the very young.

**Silent Corticotroph Adenomas** The surgical correction of high preoperative levels of PRL may enhance the likelihood of misdiagnosis of prolactinoma. The attendant hazards of this error and the importance of a prompt, accurate electronmicroscopic diagnosis are best illustrated by the following case report:

A 28 year old woman suffered rapid bilateral visual loss. Demyelinating disease was suspected, but visual field examination revealed severe bitemporal hemianopia with early macular involvement. Sellar tomography revealed thinning and destruction of the sellar floor by a soft tissue mass filling the posterior third of the sphenoid sinus. Preoperative investigation was cut short when her visual loss progressed swiftly to legal blindness. She was admitted for an emergency operation. A single blood sample taken after anaesthetic induction showed undetectable levels of LH and FSH, and a PRL of 70.2 µg/L. (normal range 5-25) Trans-sphenoidal removal of a friable, hemorrhagic tumour led to prompt and complete recovery of visual fields and acuity. As her postoperative PRL levels remained normal, no further treatment was offered at follow-up. Five months later she became pregnant. Within a month she again reported reduced vision in the left eye and a recurrent bitemporal hemianopia progressed rapidly. At this time, an EM diagnosis of the tumour removed 6 months earlier was returned as “silent corticotrophic adenoma.” At the second operation, a large recurrent tumour was selectively removed with careful preservation of normal gland. Postoperative radiation was administered during the second trimester of pregnancy; she remained well, and was delivered at full term of a healthy boy.

**Table 5: Tumours with Hyperprolactinaemia**

Prolactinoma	46
Mixed Adenoma (GH,PRL)	5
Non-secreting	3
Acidophile Stem Cell Adenoma	2
Unclassified	2
Polyhormonal (MEA I)	1
Intrasellar Arachnoid Cyst	1
	<hr/> 60

The falsely reassuring normal postoperative PRL levels in this case led to the mistaken diagnosis of prolactinoma and delayed treatment appropriate for this patient's characteristically aggressive silent corticotroph tumour—treatment which could have prevented its recurrence. The diagnosis of prolactinoma can be confirmed only by immunohistology and electron microscopy, and this confirmation should be obtained promptly after operation.

Silent corticotroph (SC) tumours are a distinct pathological entity<sup>9</sup>, but certain clinical features may induce a high index of suspicion for pre-operative diagnosis. They show a marked tendency to rapid growth, haemorrhagic infarction, and fulminant optic compromise. Three of 14 previously published cases, and 7 of our 14 current surgical cases showed hyperprolactinemia. SC adenomas are basophilic and PAS positive, and although unassociated with hypercorticism, contain variable amounts of ACTH,  $\beta$ -lipotropin, and  $\alpha$ -endorphin. Their association with hyperprolactinemia may result from a "stalk-section" effect, or alternatively, endorphin may stimulate the increased release of PRL from normal surrounding lactotroph cells.

Though SC tumours accounted for 43% of tumours of corticotrophic origin in the pathological series<sup>9</sup>, there are only 10 of 46 in our surgical series. Those of the greatest interest are associated with Cushing's disease.

### Cushing's Disease

It is uncommonly appreciated that in the classic 1932 description of the disease that now bears his name, Harvey Cushing was able to locate adenomas in only 7 of the original 12 cases collected.<sup>10</sup> While this ratio sufficed to establish his thesis, it is intriguing to speculate that his chosen subtitle, "Pituitary Basophilism," may have been left as a caveat for a wider interpretation. He described for us what would one day pose a singular surgical problem; these tumours might be of exceedingly small diameter (under 3 mm.), they might hide laterally in a recess, and they had a proclivity to burrow posteriorly into the neurohypophysis. The search for, and selective removal of these lesions remains a challenging technical problem, but current reports of extensive experience imply a high degree of early success when such a tumour is found and removed.<sup>11</sup> It has become the accepted view that the great majority, if not all cases of Cushing's disease are caused by discrete, clearly demarcated adenomas.<sup>12</sup> I will describe the measure in which our experience has differed from this account in the following brief survey of our findings in Cushing's disease, some of which have been reported earlier.<sup>13</sup>

Thirty-three patients (28 females and 5 males) ranging in age from 14 to 60 years, presented with clinical features of Cushing's syndrome. All demonstrated hypercorticism as indicated by 24-hour measurements of urinary free cortisol, and its pituitary-

dependency was inferred from low and high dose Dexamethasone suppression tests in all cases. In radiological studies the pituitary fossa was normal in 24 patients, showed subtle lateralized abnormalities in 6, and was enlarged in only 3. CT scanning demonstrated focal abnormality in 12 patients, but was normal in 15. The subsequent trans-sphenoidal operation was thus exploratory in a majority of the cases. Operation was abandoned in 2 patients because of profuse perisellar venous bleeding, and no pituitary biopsy was obtained. Of the remaining 31 patients, a discrete pituitary adenoma was the sole pathological finding in only 14. A 15th patient whose adenoma had been treated previously with proton beam therapy, was also found to harbour nests of corticotroph cells in the peritumourous gland at a subsequent second operation for hypophysectomy. Adenomatous cell nests were the only finding in 2 other patients. In 2 patients, Crooke's cell change was the only detectable abnormality. In 1 patient with a notably enlarged sella, diffuse homogeneous enlargement of the gland was the only finding. Five cases showed no pathological change in tissue resected because of suspected focal abnormality.

In two other patients with similar focal nodules, uniform hyperplastic change with a normal reticulin pattern was found with no evidence of tumour formation. Four pituitary glands, 3 of which were totally removed at elective complete anterior hypophysectomy, displayed diffuse multifocal corticotroph cell hyperplasia, interspersed with normal adenohypophysis (see figure 4).

The selective removal of solitary adenomas led to sustained remission of hypercorticism in 13 of 14 cases. This result was also achieved in 4 of the 6 patients with hyperplasia, but at the expense of complete hypophysectomy, planned preoperatively. Median wedge resection resulted in complete remission in 1 patient, but serial sectioning of this tissue revealed a 1 mm. adenoma (see Table 6).

While a few early reports<sup>14</sup> refer to findings suggestive of hyperplasia, most recent papers are lacking in evidence for a detailed pathological search for this finding using modern techniques. While we accept that hyperplasia is likely to account

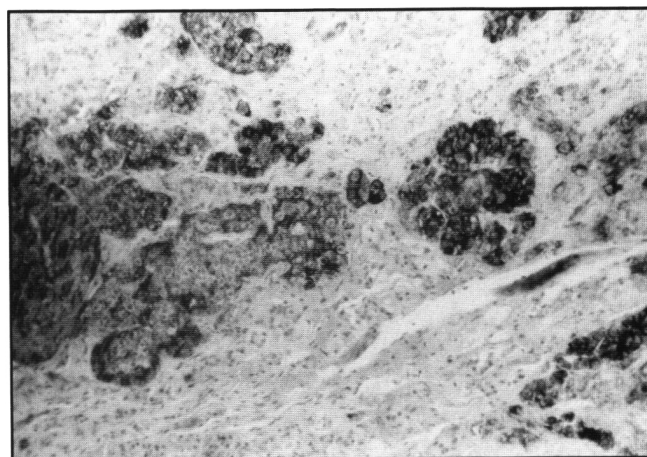


Figure 4 — Diffuse multifocal corticotroph cell hyperplasia in Cushing's disease. Immunoperoxidase technique shows ACTH-positivity in multiple, separate acini. Immunocytochemical staining and photomicrograph courtesy of Dr. Kovacs, St. Michael's Hospital, Toronto

for a minority of cases of Cushing's disease, we believe it to be more prevalent than previously suspected. The awareness of this possibility should lead, we believe, to the preoperative consideration of complete hypophysectomy in the event that no tumour is found after systematic trans-sphenoidal exploration.

**Table 6: Cushing's Disease: Correlation of Pathological Findings and Clinical Results**

Pathological Findings	No.	Remission	%
Solitary Adenoma	14	13	92.9
Adenoma + Cell Nests	1	0	0
Cell Nests Only	2	0	0
Crooke's Hyaline Change	2	0	0
Diffuse Enlargement	1	0	0
No Pathologic Diagnosis	5	1	20
Hyperplasia			
Focal Nodular	2	1	50
Multifocal Diffuse	4	3(hypophx)	75
	31	18	58.1

### CONCLUSION

The three main clinical categories of hypersecretory pituitary syndromes present as ostensibly uniform clinical populations. Each of them, however, is made up of distinguishable subtypes, each with a characteristic biology. In some instances, preoperative differentiation may be made by the recognition of an identifiable pattern of clinical and biochemical features, with important prognostic implications. In the special case of Cushing's disease, the search continues for a means of recognizing the important subgroup of cases who do not harbour tumours, but rather one or other variety of hyperplasia. Preoperative consideration of this diagnosis may dictate surgical policy. Until a reliable biochemical means of identification of these patients is found, elective total hypophysectomy should replace adenolectomy in certain selected cases of Cushing's disease, and in most if not all patients after childbearing age.

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and teaching, which has helped establish clinico-pathologic correlations and has led to the recognition of new sub-classifications within the main groups of patients with and without hypersecretory syndromes.

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