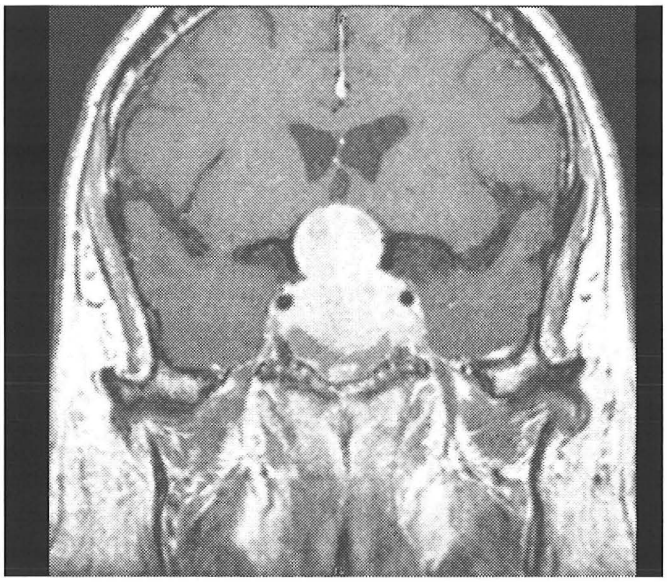
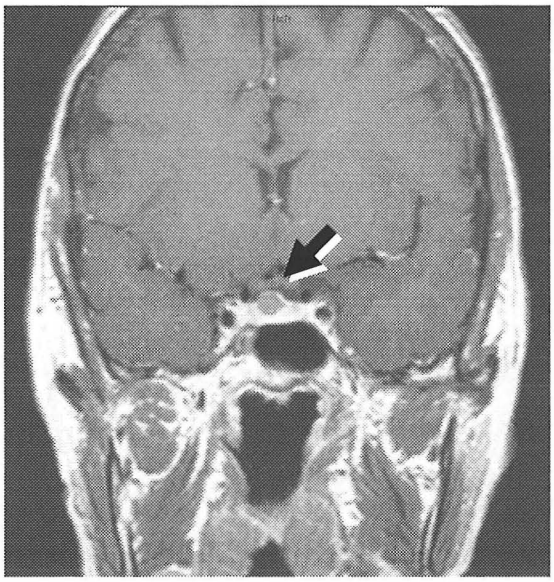
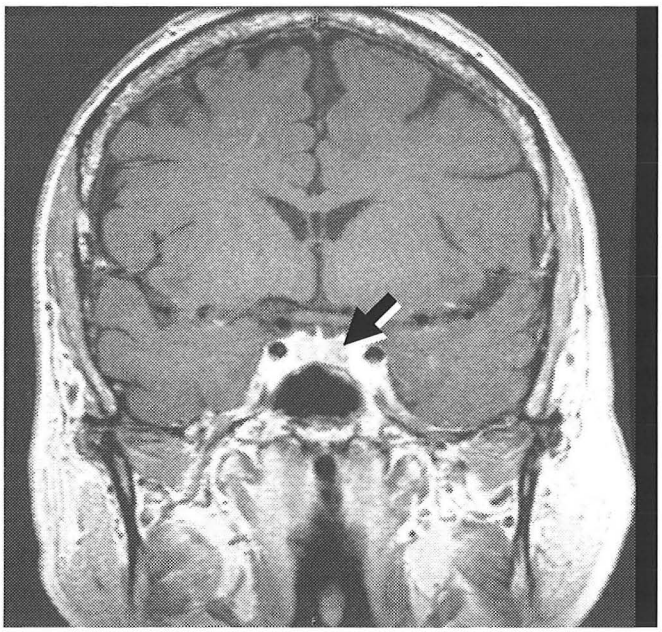
Diagnosis and Treatment of Pituitary Tumors







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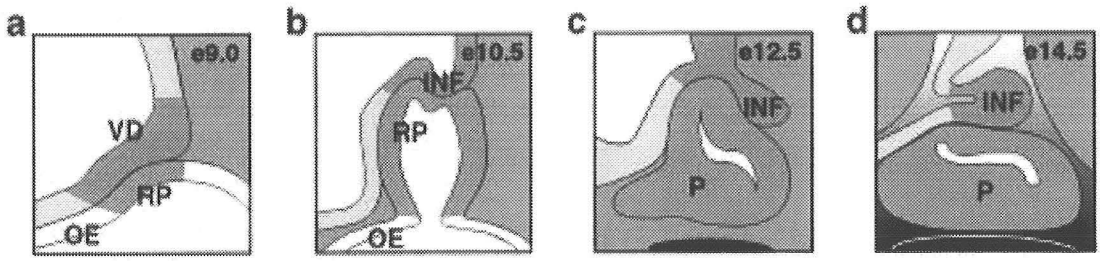
June 30, 2005

The Embryology and Composition of the Pituitary Gland

During embryogenesis, the cells that will comprise the anterior pituitary gland are derived from somatic ectoderm that overlies the neural plate-derived structures that will differentiate to form the hypothalamus and posterior pituitary gland. A highly regulated hierarchical expression of transcription factors leads to the morphogenesis and development of the mature anterior pituitary (Couly, 1988, Eagleson, 1990, Treier, 1998).



Embryology of the developing pituitary gland. RP is Rathke's pouch, OE is Oral ectoderm, P is Pituitary. The time scale of the development that is depicted here is in days of embryonic life (Treier, 1998).

The mature anterior pituitary is comprised of five distinct cell types that secrete six individual hormones.

Pituitary Hormones and Cell Types

Cell type (%)	Hormone	Size (amino acids)
Corticotrophs (20)	Adrenocorticotropin (ACTH)	39 amino acids
Somatotrophs (50)	Growth hormone (GH)	191 amino acids
Mammotrophs (10)	Prolactin (PRL)	198 amino acids
Thyrotrophs (5)	Thyrotropin (TSH)	α subunit: 89 β subunit: 112
Gonadotrophs (15)	Luteinizing hormone (LH)	α subunit: 89 β subunit: 115
	Follicle stimulating hormone (FSH)	α subunit: 89 β subunit: 115

Anatomy and physiology of anterior pituitary function

Mechanisms controlling pituitary hormone secretion

The secretion of each of the pituitary hormones is controlled by influences derived from the hypothalamus and by circulating modulators. The mechanisms controlling the synthesis and secretion of each is complex and is only briefly outlined in this discussion. Certain features are common however: multiple trophic inputs, the existence of feedback loops and peripheral modulators. In most instances, the secretion of anterior pituitary hormones is controlled by response to a **positive** trophic stimulus that is delivered to the cells of the anterior pituitary via the portal vessels.

Regulatory Influences controlling Pituitary Hormone Secretion

Cell Type	Pituitary Hormone	Positive Hypothalamic Regulator	Negative Hypothalamic Regulator	Feedback Modifier
Corticotrophs	ACTH	**CRH**		Cortisol
Somatotrophs	GH	**GHRH** GHS		IGF-1
Mammotrophs	PRL	TRH	**Dopamine**	Prolactin
Thyrotrophs	TSH	**TRH**		T_4, T_3
Gonadotrophs	LH	**GnRH**		Sex steroids
	FSH	**GnRH**		

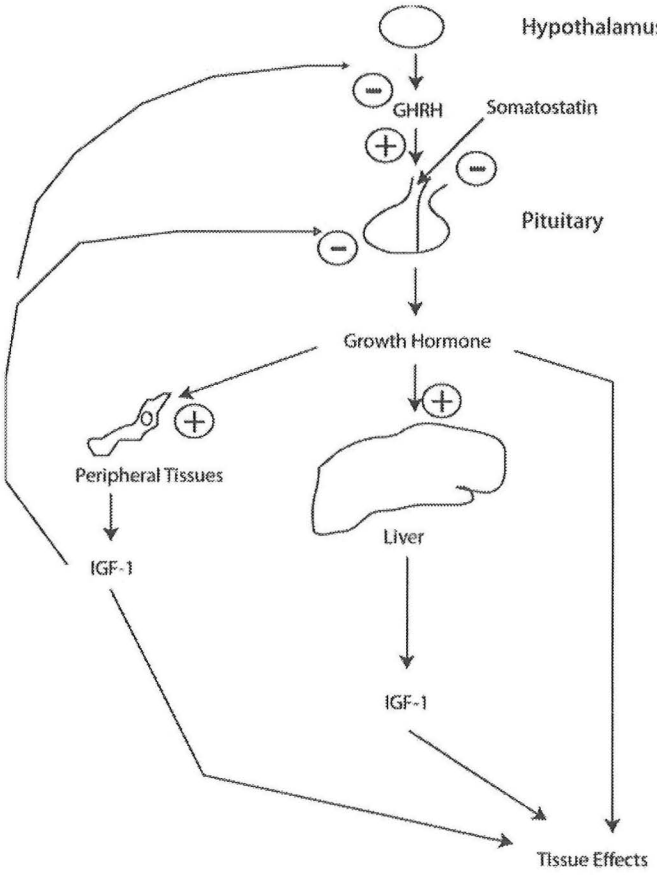
GHS – growth hormone secretogogues

Growth hormone (GH) is representative in this regard, responding with an increase in the secretion of GH to the delivery of Growth Hormone Releasing Hormone (GHRH) to the somatotrophs of the anterior pituitary. In the case of GH, this effect of GH is counterbalanced by a negative influence of somatostatin on GH secretion. Although GH is believed to exert direct effects in peripheral tissues, it is also clear that many of the effects of GH are mediated by the stimulation of Insulin-like Growth Factor I (IGF-1; a.k.a. Somatomedin C) in the liver and in peripheral tissues. IGF-1 serves to exert the effects of GH in peripheral tissues and also serves to feedback to regulate the secretion of GH by the pituitary. Importantly, as GH secretion is pulsatile, both in normal humans and in patients with pituitary tumors, IGF-I can serve as a surrogate measure of the secretion of GH integrated over time.

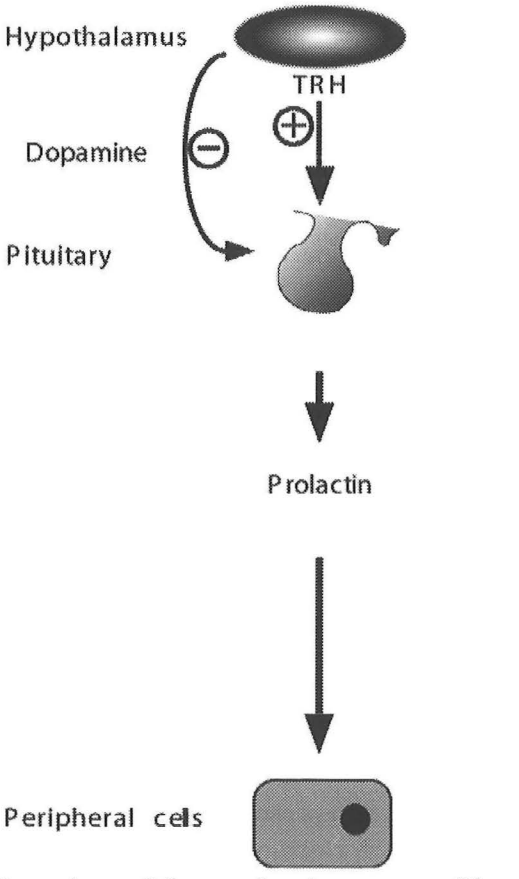
GHRH is delivered to the anterior pituitary via the long hypophyseal portal vessels and binds to specific GHRH receptors on the surface of somatotrophs. As the result of GHRH binding, intracellular signaling

cascades are activated, including the stimulation of adenylate cyclase. This increase of cAMP levels stimulates both the synthesis and secretion of GH. Somatostatin binds to five distinct receptors serves to antagonize this effect at both the transcriptional and at the level of hormone secretion. These influences are modulated additionally by influences of endogenous GH secretogogues, such as GHrelin.

Finally, the level of GH is regulated by feedback loops that involve the feedback regulation of GH production at both the hypothalamic and pituitary. In the hypothalamus, IGF-I increases the secretion of somatostatin and suppresses the secretion of GHRH. At the level of the pituitary, IGF-I inhibits synthesis and release. Importantly, as IGF-I exists in serum complexed to binding proteins, the biological effects are mediated by the levels of free IGF-I (Chen, 2005). Although attenuated, many characteristics of GH secretion and feedback (such as feedback inhibition by IGF-I) are maintained in GH-secreting tumors (Jaffe, 2001).



Overview of the mechanisms controlling Growth Hormone secretion



Overview of the mechanisms controlling Prolactin secretion

Pathogenesis of pituitary tumors

In the past, the pathogenesis of pituitary tumors had been the subject of some debate, centering on the possibility that the aberrant growths might be derived from abnormal trophic influences that are derived from the hypothalamus or clonal genetic events derived from mutations within the cells of the anterior pituitary. Examinations of a number of different tumor types have established that such tumors are monoclonal in origin, representing clonal populations that escape the normal mechanisms regulating the growth of the cells of the anterior pituitary (Herman, 1990, Alexander, 1990, Gicquel, 1992, Schulte, 1991).

The demonstration that anterior pituitary tumors are clonal in origin led to investigation of the mechanisms by which the normal mechanisms of growth are dysregulated. The first of these investigations to bear fruit centered on an examination of the signaling mechanisms controlling GH secretion. Model systems employing cells isolated from the rat pituitary demonstrated that in culture, GHRH stimulated and somatostatin inhibited adenylate cyclase activity and that these alterations had profound effects on both the secretion and growth of somatotrophs. Subsequent investigations demonstrated that a subtype of human GH-secreting adenomas behaved in a fashion consistent with a dysregulation of adenylate cyclase (Vallar, 1987).

Tumour		Adenylyl cyclase (pmol cAMP mg^{-1} min^{-1}) Basal	AlF_4^-	DNA	Codon 201	Codon 227
Group 1	1	13	170	Genomic	Arg	Gln
	2	6	96	Genomic	Arg	Gln
	3	16	300	Genomic	Arg	Gln
	4	43	130	Genomic	Arg	Gln
Group 2	5	170	130	cDNA	Arg (2)/Cys (3)	Gln
				Genomic	Arg/Cys	Gln
	6	480	260	cDNA	Arg (0)/His (4)	Gln
				Genomic	Arg/His	Gln
				Genomic (blood)	Arg	Gln
	7	190	130	cDNA	Arg (0)/Cys (3)	Gln
				Genomic	Arg/Cys	Gln
	8	180	120	cDNA	Arg	Gln (0)/Arg (3)
				Genomic	Arg	Gln/Arg
				Genomic (blood)	Arg	Gln

The molecular basis of this abnormality was identified as abnormalities of the regulatory G proteins: in those tumors in which an activating mutation of the Gsα protein subunit occurred, the signaling pathways within the tumors resembled that in which the tumor had been activated by trophic stimuli (e.g. GHRH) (Landis, 1989). Subsequent studies demonstrated that tumors of this type can be detected in ~40% of GH-secreting tumors. Interestingly, the tumors carrying these activating mutations displayed clinical properties similar to those in which such mutations are not detected (Landis, 1990). Finally, it is important to note that the pathways of signaling also demonstrate that the inhibitory effects of somatostatin are preserved, even in the context of activating G protein mutations.

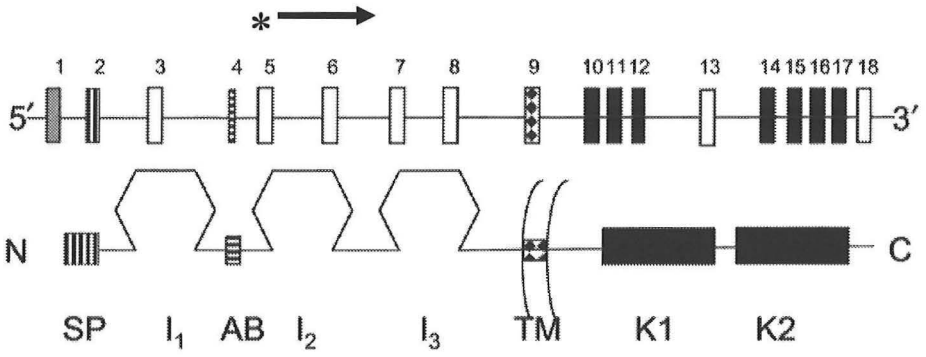
MEN1

Multiple Endocrine Neoplasia (MEN1) is associated with a triad of neoplasms, including primary hyperthyroidism, pancreatic tumors, and pituitary tumors. In 1997, the gene responsible for the development of this disorder was identified by positional cloning. The genetics of this disorder conformed to the pattern expected for a tumor suppressor. Individuals inheriting the MEN1 mutant allele via germline transmission were predisposed to develop tumors in the affected tissues when the remaining copy of the MEN1 locus was subjected to somatic mutation.

Interesting, the function of the protein encoded by the MEN1 gene, menin, has not been conclusively defined. The evidence that is available to date demonstrate that abnormalities in cell proliferation can be recapitulated in animal models (rodents and flies). Its role appears to be more general in terms of leading to the expansion playing dual roles, involved in both regulation of cell growth pathways (via interaction with other components regulating cell proliferation) and the regulation of genome stability and DNA repair. This latter set of observations dovetails nicely with early reports documenting chromosomal abnormalities in lymphocytes from patients with MEN1. Thus, the abnormalities in this protein appear to be more related to the emergence of clonal expansion of abnormal cells, rather than to an abnormality related to altered regulation of specific cell types within the anterior pituitary. In keeping with this, the distribution of cell types / tumor types is similar in tumors associated with the MEN1 syndrome and in sporadic tumors. Alterations in the MEN1 gene appear to be rare in sporadic pituitary tumors.

FGF

The mechanisms identified by which Gs_{α} subunit mutations activate somatotroph proliferation and GH secretion are a dramatic extension of the principles that govern the normal secretion of GH. This being said, these alterations account for only a subset of GH-secreting pituitary tumors. A wide range of investigations have attempted to define the molecular events of pituitary tumor development. An interesting group of studies have been published by the group of Ezzat et al. In their initial report, these authors identified a truncated form of the FGF receptor 4 (ptd-FGFR4) that was expressed in a number of pituitary tumors. In transgenic studies, these authors demonstrated that the expression of ptd-FGFR4 in the lactotroph lineage resulted in the development of prolactin-secreting tumors (Ezzat, 2002). This truncated form of FGFR4 can be detected in ~ 60% of adenoma samples, but is not detected in the normal pituitary (Qian, 2004).



Schematic of the structure of FGF-R4 protein and gene. The species detected by Ezzat and colleagues is initiated in exon 5 (*) and produces an FGFR4 that is truncated in its extracellular domain (Ezzat, 2002).

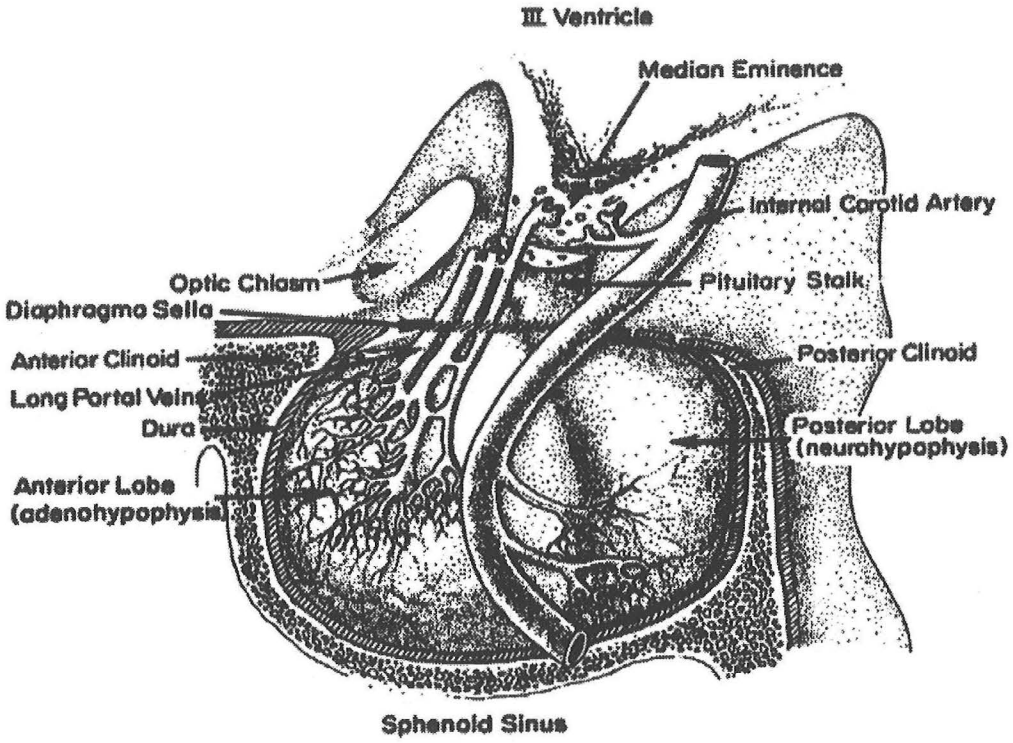
Genetic Mutations Identified in or Associated with Pituitary Adenomas

Gene	Type of Mutation	Type of Effect	Human Disorder	Occurs in sporadic tumors?
Category: Gain of Function				
Gsα	Germline and somatic mutations	Activation of somatotroph growth and secretory activity	GH-secreting	Yes, ~40%
ptd-FGFR4	Truncated, active FGFR4	Stimulation of cell growth	All except prolactin-secreting	Yes, ~60%
Category: Loss of Function				
MEN1			MEN1	Rare

Summary

A wide range of mechanisms have been explored in an attempt to identify the pathogenesis of pituitary tumors (reviewed in Asa, 2002). Of these, only the activating mutations of Gsα appear to occur frequently in sporadic (non-familial) tumors and are clearly related to the alterations of growth and GH secretion of GH secreting pituitary tumors. Such mutations are largely restricted to the somatotroph lineage. The expression of truncated forms of the FGFR4 can cause tumors in transgenic mice, but the importance of this in the pathogenesis of human adenomas has not been established.

3. **Presentation and differential diagnosis**



Anatomy of anterior and posterior pituitary

The proximity of the anterior pituitary to the surrounding structures in many instances dictates the presentation of an individual patient. The following discussion focuses on three different categories: 1) incidental discovery, 2) symptoms/ sign secondary to mass effect, and 3) syndromes of hypersecretion.

The discovery of a mass in the anterior pituitary requires a consideration of potential etiology. A range of potential etiologies should be considered, including benign tumors, cysts, inflammatory lesions, and malignant tumors.

Differential diagnosis of pituitary masses

Benign Tumors	
	Pituitary adenomas Craniopharyngiomas Meningiomas
Cysts	
	Rathke's cleft cysts
Infiltrative / inflammatory processes	
	Lymphocytic hypophysitis Histiocytosis
Malignant tumors	
	Primary Metastatic
	Lung Breast

An idea of the proportion of patients with each of these disorders in individuals discovered to have a pituitary lesion incidentally can be gleaned from a small number of series.

In some instances, this information is derived from autopsy series. In one reported series, the incidence was estimated by a review of existing autopsy series in the literature. This examination yielded a derived incidence of ~15% for microadenomas. The inferred incidence of undetected macroadenomas was at least 30 fold lower. Radiographic studies detect signal abnormalities, such a focal areas hypointense areas much more frequently.

Autopsy series	
	Microadenomas: 10-20%
	Macroadenomas: < 0.05%
Autopsy	
	> 2 mm: 6%
MRI studies	
	Up to 40% had focal hypointense areas

Molitch, 1990, Teramoto, 1994

In the retrospective review reported by Sanno et. al. (Sanno, 2003), the information was derived by examining the records of 506 patients were examined retrospectively from 71 institutions in Japan to examine the behavior and subsequent outcomes of patients identified as having 'endocrinologically silent' pituitary masses. The masses were identified during CT or MRI exams

performed for unrelated symptoms, such as headache (37%), 'brain checkup' (13%), vertigo (12%), and head injury (7%).The patients identified in this fashion were found to have been handled in two ways: either 1) managed medically / watchful waiting, or 2) managed surgically. The principal determination of the therapy used in these two groups was based upon the size and positioning of the tumor and upon the patient's inclination.

General Characteristics of the Population

Average size – 27 mm.	
No patient had hormonal hypersecretion (patients with VF abnormalities were excluded)	
258 underwent surgery	Supra sellar extension, size, patient desires
	Histology available
248 were followed (mean 26.9 months; range, 6 to 173)	Follow-up: 0.5-176 months (average 26.9) Average size: 13.2 mm
No patient had hormonal hypersecretion (patients with VF abnormalities were excluded)	

Sanno N Eur J Endocrinol 149: 123-127, 2003

Histological and Presumptive Diagnoses

Surgical	(n = 258)	Nonsurgical	(n = 248)
Non-functioning Pituitary tumor	81%	Non-functioning Pituitary tumor	46%
Rathke's cyst	16%	Rathke's cyst	39%
Arachnoid cyst	2%	Arachnoid cyst	1%
Craniopharyngioma	1%	Other cyst	3%
		Hypertrophy	2%
		Craniopharyngioma	0%
		Hypophysitis	0.4%
		Other	18%

Sanno N Eur J Endocrinol 149: 123-127, 2003

Changes during the subsequent follow-up period

	Number of patients (%)	Initial size	<10mm	>10mm	Length of FU	No. w/ surgery
Increased in size	30 (12)	13.9	10	20	45.5 (2-173)	6
	23 pit tumors 5 Rathke's 2 other					
Decreased in size	29 (12)	13.7			34.7 (5-98)	
	11 pit tumors 15 Rathke's 3 other					
No change	180 (74)					4

While the series reported by Sanno is the largest clinical series of patients, the retrospective nature of this study and the fashion in which patients were identified may have contributed to a skewing of the results. In other studies (Feldkamp, 1999), a smaller number of patients (n = 50) were identified were followed for an average observation period of 2.7 years.

Follow-up results of 50 patients referred with pituitary adenomas

	Microadenomas	Macroadenomas
No change	29 (94%)	13 (69%)
Increase	1 (3%)	5 (26%)
Decrease	1 (3%)	1 (5%)
Total	31	19

Symptomatic - Symptoms and signs that can be associated with all pituitary tumor types

The growth and enlargement of tumors of the anterior pituitary can manifest in a number of different patterns, dictated principally by the direction of growth. Patients whose tumors grow superiorly out of the sella will impinge on the optic chiasm and will present with visual impairment, most often detected first in the upper outer visual quadrants. In patients without symptoms attributable to hormone excess, this is the most common presentation.

Much less frequently, patients may display evidence of cranial nerve impingement (reflecting invasion of cavernous sinus), effects on memory (reflecting invasion beyond the cavernous sinus into the temporal lobe), or CSF rhinorrhea (reflecting growth inferiorly and erosion of the sella floor). Infrequently, the first symptoms may be related to hemorrhage into the tumor itself (headache +/- a rapid change in visual fields).

Symptoms and signs associated with specific pituitary tumor types

Prolactin

Prolactin secreting adenomas are the most common type of pituitary tumor, accounting for ~2/3 % of pituitary tumors that present clinically. Variations in the frequency of this tumor type among the different reported series reflect differences among the populations surveyed (referral centers, Ob-Gyn patient populations, etc.). Clinical manifestations encompass a spectrum of presentations, ranging from patients manifesting symptoms attributable to mass effect (visual field changes, hypopituitarism) to those related to galactorrhea or to oligo / amenorrhea. The proportion of patients in these different categories will reflect in part the ages, reproductive status, and sex of the patients.

	Women – Pre-menopausal	Women - Post- menopausal	Men
Galactorrhea	Frequent	Infrequent ‡	Infrequent ‡
Oligo / amenorrhea	Frequent	----	----
Mass effect	Rare†	Common	Common

† - The rarity of this presentation reflects the capacity of prolactin to cause of menstrual cycle abnormalities with even modest elevations of prolactin (≥ 40 ng/mL), precipitating evaluation at small tumor size (exceptions: S/P hysterectomy; oral contraceptives).

‡ - The rarity of this presentation reflects the requirement for estrogen in addition to prolactin for milk production.

Acromegaly

Of the hormonally active pituitary tumor types, GH-secreting pituitary tumors are the second most frequent, accounting for 20 % of pituitary tumors. GH-secreting pituitary tumors may cause a number of different clinical manifestations, as depicted in the table below. While not well established in the literature, the specific manifestations often reflect influences reflecting duration, extent of hormonal elevation, and family history.

Frequency of Symptoms and Signs in Patients with Acromegaly

Finding	Present/Total
Recent acral (soft tissue) growth Ring and shoe size changes out of proportion to changes in overall body mass	57/57
Arthralgias	41/57
Excessive sweating	52/57
Weakness	50/57
Malocclusion	39/57
New skin tags	33/57
Hypertension	21/57
Carpal tunnel syndrome	25/57
Elevated fasting blood sugar	17/57
Headache	~10%

Cushing's disease

ACTH-producing pituitary tumors are among the rarest of the hormonally active pituitary tumor types. They are also the most problematic tumors, from both a diagnostic and therapeutic standpoint. This relates to two separable issues. First, is its often subtle manifestations and the insidious nature of its onset; second, it the broad overlap of its clinical features with traits that are widely present in the general population (and apparently unrelated to syndromes of glucocorticoid excess).

Frequency of Symptoms and Signs in Patients with Cushing Syndrome

Sign or Symptom	Reported incidence (%)
Centripetal obesity	79-97
Facial plethora	50-94
Glucose intolerance	39-90
Weakness, proximal myopathy	29-90
Hypertension	74-87
Psychological changes	31-86
Easy bruisablity	23-84
Hirsuitism	64-81
Abdominal striae	51-71

Evaluation & Diagnosis

Incidental Pituitary masses (Incidentalomas)

The management of patients with incidentally discovered pituitary masses will depend - at least in part - on the size and character of the lesion. Lesions 10 mm or larger are more likely to be associated with visual and hormonal abnormalities at the time of discovery. This class of lesions is more likely to enlarge on follow-up than smaller lesions, particularly those that display radiographic characteristics compatible with nonfunctioning pituitary adenomas.

In the study of Sanno et al. (Sanno, 2003), the size of the sellar mass increased in 30 (20 of the 123 with presumed macroadenomas and 10 of the 57 with presumed microadenomas). Among the 10 microadenomas that increased in size, only three (all > or =5 mm) increased to >10 mm in 65 to 84 months of observation. Outcome also varied with presumed diagnosis: of 115 presumed adenomas, 20% showed increase in size; by contrast, only 5 % Rathke's cysts enlarged (mean follow-up 4 years).

In a two year prospective study of 67 patients with pituitary incidentalomas, tumor enlargement was seen in seven of 25 macroadenomas, but in only one of 42 microadenomas (Feldkamp, 1999).

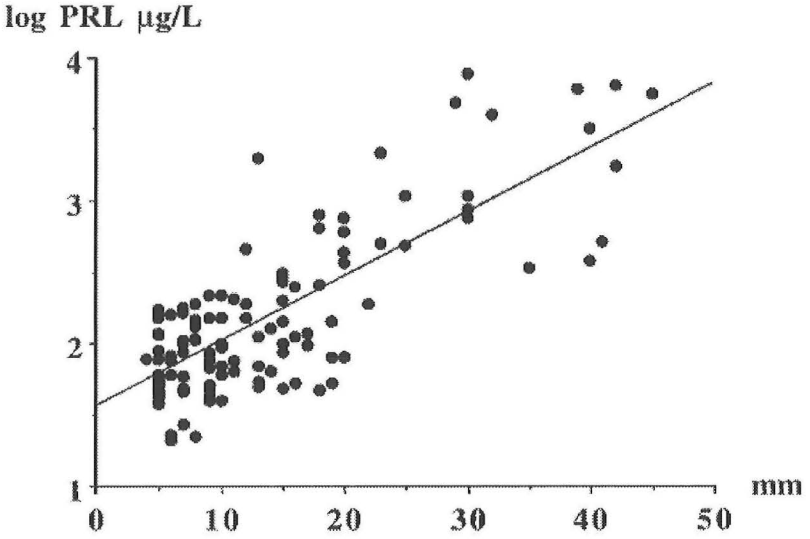
Based on such information, the recommendations for follow-up of incidentally discovered lesions vary with the size of the abnormality:

Size >10 mm: careful evaluation for evidence of visual field impairment and for hormonal hypersecretion; if surgery not indicated, careful follow-up is appropriate every 6-12 months (VF, MRI, selected endocrine testing)

Size < 10 mm: prolactin only in patients with no evidence of hormonal excess; follow-up MRIs indicated only for larger lesions. This paradigm is consistent with cost benefit analyses that have been published (King, 1997)

Hyperprolactinemia

In most instances, single measurements of prolactin can be used to identify patients with elevations of prolactin and more complicated sampling regimens are not required. Minor elevations of prolactin (particular <150 ng / mL) should elicit a careful review to identify medications and / or conditions that will interfere with the normal tonic dopaminergic tone that inhibits prolactin secretion.



From Losa et al, JCEM 87: 3180–3186, 2002

In patients with pathological elevations of prolactin, it is critical to recognize that there should be a relationship between the level of elevation of prolactin and the size of the tumor identified. This is particularly important in setting the expectation of the patient and physician. A tumor that is not a prolactinoma can be associated with an elevated prolactin, if the tumor compromises the delivery of dopamine to the normal somatotrophs of the residual pituitary. In such a n instance, normalization of the prolactin will likely be possible using dopamine agonists, but will not likely affect the growth of the tumor.

Acromegaly

In most instances the clinical features of the patients will suggest the diagnosis and laboratory testing will be conducted only to confirm the diagnosis. Laboratory tests to confirm the diagnosis can employ measurements of IGF-I and GH. In instances where the diagnosis remains in doubt, measurements of GH following glucose suppression can be employed (Chapman, 1994).

It is important to recognize that the normative ranges vary in an age- and sex-dependent fashion for IGF-I. Further, it is quite clear that the IGF-I assays that are currently available commercially can be misleading, particularly in subtle cases. In instances where clinical suspicion is high, measurements of glucose-suppressed GH may be required.

Cushing's syndrome

The diagnosis of Cushing's syndrome and the correct identification of its cause are arguably among of the greater challenges in endocrinology. For the purposes of this discussion, only a few simple guides are appropriate.

Based on initial clinical suspicions, the diagnosis of Cushing's syndrome should be investigated by any screening test: either overnight dexamethasone suppression test or measurements of urinary free cortisol are appropriate. If measurements of UFC are employed, it important to recognize that assay methods vary widely between laboratories. The most consistent assays are those that employ HPLC methodology. Such assays are readily available commercially (but may need to be specifically requested) and are much more reproducible compared to immunological methods. After establishing that Cushing's syndrome is present, ACTH measurements are conducted to determine whether the entity is ACTH dependent (Cushing's disease or ectopic ACTH production) or independent of ACTH (i.e. autonomous adrenal production of cortisol).

Treatment

The treatment of pituitary tumors can be broadly divided into two categories based on tumor types: 1) those that secrete prolactin, and 2) those that do not. This discrimination is based upon the availability of medications that are able to effectively manage prolactinomas medically in the vast majority of cases and the lack of similar agents for all other tumor types.

Surgery

Medical therapy capable of effectively controlling both hormonal hypersecretion and tumor growth is only available for prolactin secreting tumors. Despite this, some authors have continued to consider whether the surgery is appropriate first line therapy. This debate has centered principally on the drawbacks that accompany medical therapy: need for the continued 'life-long' therapy, side-effects of medical therapy, and resistance to DA that is observed in some tumors. Although such issues have engendered discussion in the literature (Molitch, 1997; JEI 23: 122-124, 2000), most authors have been dissuaded by the reported high recurrence rates of patients with prolactinomas treated with surgery as first line therapy, ranging as high as 40%.

	Tumors operated		Tumors cured		Recurrence	
	Micro	Macro	Micro	Macro	Micro	Macro
Mollitch	1321	1279	973 (73)	415 (32)	114/544 (21%)	50/253 (19.8%)

	Recurrence	Follow-up (months)
Tyrell, et al., 1999	20/132 (15%)	187(microadenomas)
		38 (macroadenomas)
Losa, et al. 2005		50

This issue has been recently examined in prospective analyses at single referral centers. The results have been demonstrated impressive rates of long-term cure, particularly with small intrasellar lesions (Losa, 2005; Tyrell, 1999). The finite but low rates of mortality and morbidity have continued to argue favorably for medical therapy (Molitch, 1997).

As effective medical therapy capable of effectively controlling both hormonal hypersecretion and tumor growth is not available for prolactin secreting tumors, surgery remains the primary mode of therapy for all tumors other than prolactin-secreting tumors.

Primary outcomes of surgical series

Surgery is an effective therapy for all types of tumors, those that are functional and those that are non functional. Long-term outcomes are available from a number of centers, including large series compiled by individual surgeons. It is clear from an inspection of these series that the principal determinant dictating long-term remission is the extent of tumor involvement at the time of surgery.

	n (%)
Grade	
Relationship of adenoma to sella and sphenoid sinuses	
I: sella normal or focally expanded; tumor <10 mm	17 (7)
II: sella enlarged; tumor ≥10 mm	173 (70)
Sphenoid	
III: localized perforation of sellar floor	34 (14)
IV: diffuse destruction of sellar floor	22 (9)
Distant spread	
V: spread via cerebrospinal fluid or blood	0
Stage: extrasellar extension	
Suprasellar extension	
0: none	91 (37)
A: occupies cistern	55 (22)
B: recesses of 3rd ventricle obliterated	35 (14)
C: 3rd ventricle grossly displaced	22 (9)
Parasellar extension	
D: intracranial (intradural)	1 (0.4)
E: into or beneath carvernous sinus (extradural)	42 (17)

From Abosch, 1998

	0	A	B	C	D	E
Stage						
Percent of all patients with persistent disease	34	13	10	16	1	25
Percent of patients in each stage with persistent disease	30	18	23	59	100	48
Grade	I	II	III	IV		
Percent of all patients with persistent disease	5	57	18	20		
Percent of patients in each grade with persistent disease	24	26	41	73		

From Abosch, 1998

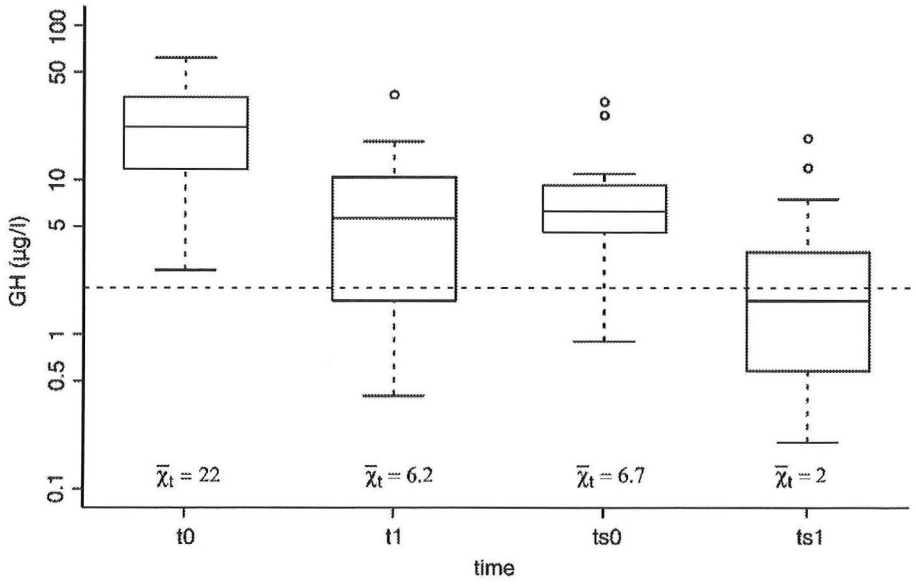
With respect to outcomes reported for GH-secreting tumors is the diversity with which investigators define 'cure'. In the series of Nomikos et al (Nomikos , 2005), the authors employed a rigorous definition that included measurements of GH, glucose-suppressed GH and IGF-I. In these investigations, they were able to achieve long-term cures of ~60%. In many other series (Nomikos et al, 2005, and cited within), definitions have been employed that are much less rigorous (e.g. random GH measurements below 2.5 or 5 ng/mL).

Similar outcomes have been reported for other tumor types, such as ACTH-secreting pituitary tumors (Hammer, 2004). In such analyses, as with GH-secreting adenomas, tumors with advanced stages (i.e. extension beyond the sella) had a much greater likelihood of having persistent disease. In keeping with the small size of ACTH-producing pituitary adenomas, a higher proportion of patients with low grade localized ACTH-producing tumors have persistent disease, reflecting unsuccessful initial localization.

Use of surgery as an adjunctive measure

In addition to the use of surgery as a sole therapy with an intent to effect a cure, limited studies have also examined the used of surgery to improve the control achieved with somatostatin analogues (Petrossians, 2005).

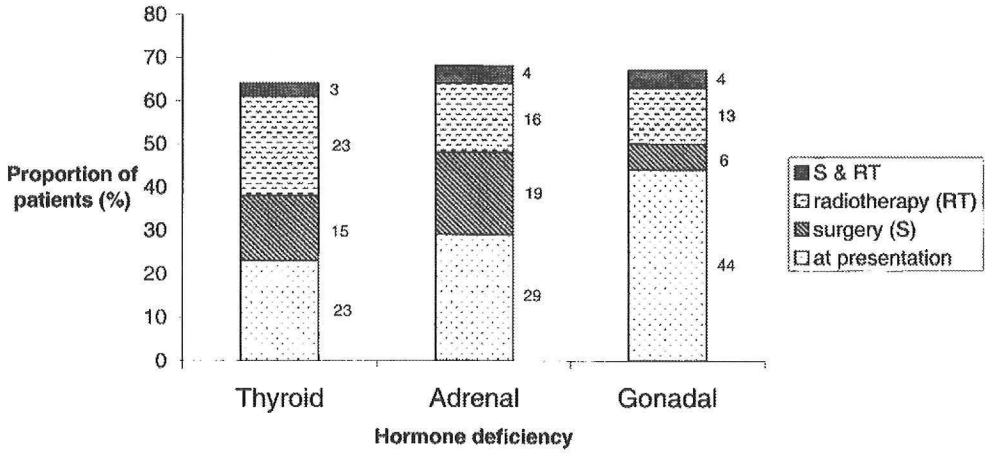
This study assessed the control achieved - preoperatively and post operatively - using somatostatin analogues in large invasive GH-secreting pituitary tumors. As depicted in the figure, the control achieved in this subgroup of patients was improved in the patients following debulking of their tumor. These observations are consistent with studies of patients treated with somatostatin analogues, which demonstrated better control in patients with lower GH levels (Bevan , 2002). While limited in scope, demonstrate that debulking may be of benefit to the long-term management of patients in whom a curative resection in not possible.



From Petrossians, 2005

Radiation

A number of different modalities exist to irradiate pituitary tumors, including conventional fractionated radiotherapy and methods to deliver radiation doses stereotactically. Although such methods are generally not employed as first line therapies for patients with pituitary tumors, they represent modalities that are useful for treating patients with residual or recurrent disease.



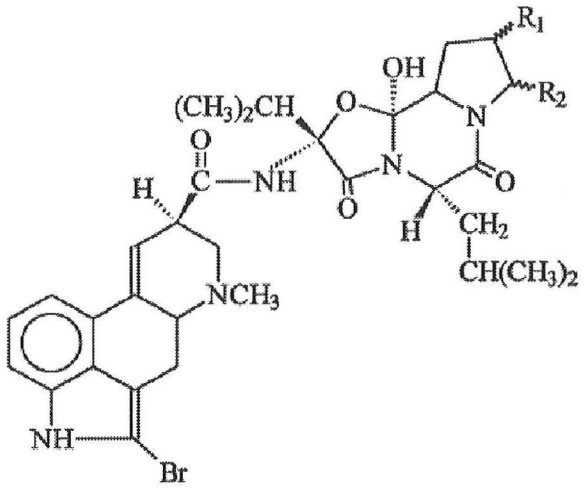
From Boelaert et al, 2001

In any event, in addition to the need to monitor patients to assess the control or progression of their disease (as assayed by measurements of hormone secretion or tumor growth), it is also critical to anticipate the development of pituitary hormone deficiencies.

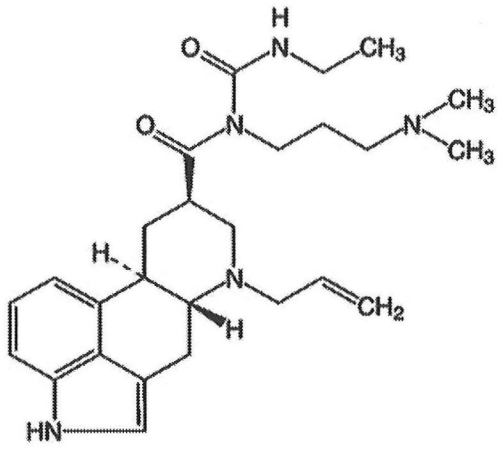
Medical therapy

Dopamine agonists: Prolactin-secreting tumors

Parlodel (bromocriptine) was introduced in 1971 for the treatment of hyperprolactinemia and was quickly established as first-line therapy in most patients (Bevan, 1992). Application in a variety of patient groups documented that virtually all patient with hyperprolactinemia will respond to Parlodel with a decrease in prolactin levels. In patients with small tumors, normalization or resumption of normal menses was documented in 80-90% of patients . This response was paralleled in series examining patients with larger tumors which demonstrated reductions of tumor volume of > 50% after 12 months of therapy.



Parlodel
(Bromocriptine)
R_1 and R_2 are H



Dostinex
(Cabergoline)

Despite its efficacy in the vast majority of patients, characteristics of this drug limited its use by patients, particularly its pharmacokinetics and its side effect profile. Bromocriptine, with a half life of ~2-3 hours, required b.i.d. dosing or t.i.d. dosing to achieve maximal efficacy. More importantly, its side effects, primarily nausea and orthostatic dizziness, could be severe particularly in young women, a group in which the drug is frequently employed. For this reason, the approval of Dostinex (cabergoline) for use in the US in hyperprolactinemia was welcome. Although structurally quite closely related to Bromocriptine, the drug shows substantially slower kinetics of inactivation, permitting weekly or twice weekly administration.

The table below summarizes a range of series in which cabergoline was employed to treat patients with various forms of hyperprolactinemia. Over all, these studies demonstrate the ability to normalize prolactin in ~84% of treated patients. Although the number of patients reporting side effects is substantial (average 28%), these side effects are much milder. This is reflected in the vary low proportion of dropouts, despite the inclusion in these series of a substantial number of patients unable to tolerate Parlodel. Of note, in these series Cabergoline displayed these impressive results despite the inclusion of a proportion of tumors that did not respond to Parlodel. In a limited number of series, the increased efficacy of Cabergoline compared to Bromocriptine has been demonstrated (Colao, 1997) or inferred (Di Sarno, 2001). As the mechanisms reported for 'resistance' to bromocriptine have involved changes in the density of dopamine receptors or alterations of post-receptor signaling, it is not clear how such differences in response might be mediated. Changes in bioavailability (as the result of slower kinetics of metabolism) and improved compliance seem likely to be contributing factors.

Overview of efficacy and tolerability of cabergoline in patients with hyperprolactinemic disorders

Series	Micro-/ macro-adenoma	% PRL normalized	% Side effects	% Dropouts	% Tumor reduction†	Bromocriptine-resistant/ intolerant
Ciccarelli, 1989	27 /3	81%	48%	11%	71%	0 /7
Ferrari, 1989	38 /8	85%	15%	0	83%	
Ferrari, 1992	108 /19	90%	23%	0	79%	10 /1
Webster, 1993	161 /1	92%	40%	3%		0 /27
Webster, 1994	223 /0	83%	68%	3%		
Pascal-V, 1995	60 /0	93%	52%	3.3%		
Biller, 1996	0 /15	73%	Minimal	0	73%	5 /5
Ferrari, 1997	0 /65	61%	25%	4.7%	66%	16 /32
Muratori, 1997	26 /0	96%	24%	0	68%	
Colao, 1997	8 /19	85%	22%	0	48%	27 /0
Colao, 1997	0 /23	83%	4%	0	61%	6 /2
Verhelst, 1999	249 /181	86%	13%	3.9%	67%	58 /140

(Modified from Verhelst, 1999)

† Criteria as to what represents significant changes is size differs between the studies.

Importantly, additional studies have demonstrated that the effects are lasting and generalizeable to other patient subsets, including men with large prolactinomas (Colao, 2004).

How long do you treat?

As detailed in the preceding sections, patients with a variety of hyperprolactinemia can be safely and effectively treated with dopamine agonists. Given these beneficial effects, it has not been clear as to the length of time that patients should be treated. Until recently, this question was answered by anecdotal experiences suggesting that these agents could be withdrawn safely in a subset of patients. The work of Calao et al (Colao, 2003) represents a first attempt to formally address this issue. In this series, these investigators examined the effects of cabergoline withdrawal in a large series of patients with no tumor, small tumors and macroprolactinomas. Although the patients subjected to this withdrawal were carefully selected (normalization of prolactin levels, lack of involvement of impingement on vital structures, no increase in prolactin following decrease of cabergoline to 0.5 mg per week), the authors demonstrated alack of recurrence of 24, 30, and 35% in patients with non-tumoral hyperprolactinemia, microprolactinoma, and macroprolactinoma,

respectively. In these groups, the 'no recurrence group' had been observed for 24-60, 24-60, and 18-60 months.

Characteristic	Nontumoral Hyperprolactinemia			Microprolactinomas			Macroprolactinomas		
	Recurrence	No Recurrence	P Value	Recurrence	No Recurrence	P Value	Recurrence	No Recurrence	P Value
Patients — no. (%)	6 (24)	19 (76)		32 (30)	73 (70)		25 (36)	45 (64)	
Sex — no.						0.02			0.74
Female	6	19		25	69		14	23	
Male	0	0		7	4		11	22	
Age — yr									
Range	26–55	18–30	<0.001	19–62	15–66	<0.001	19–70	19–66	0.52
Median	35	28	<0.001	35	28	<0.001	44	50	0.20
Prolactin — μg/liter									
Base line	69.3±5.5	68.3±11.3	0.8	179.3±37.6	154.7±50.6	0.01	935.1±859	904.8±1652	0.93
Nadir with cabergoline	9.8±2.6	1.6±0.8	<0.001	10.1±5.8	4.1±3.6	<0.001	7.3±3.6	4.1±1.9	<0.001
Prolactin suppression — %	85.4±4.6	97.4±0.9	<0.001	94.2±5.0	97.1±5.0	0.005	98.7±1.0	98.9±0.6	0.34
Maximal tumor diameter — mm									
Base line	—	—	—	6.9±1.4	6.8±1.7	0.8	18.4±4.8	16.4±7.1	0.22
Smallest	—	—	—	1.7±1.6	1.0±1.5	0.038	3.7±4.0	1.4±2.5	0.003
Tumor reduction during treatment — %	—	—	—	75.1±23.8	85.2±20.9	0.003	79.9±21.8	90.2±16.6	0.03
Median duration of cabergoline therapy — mo	48	36	0.1	48	36	0.009	48	36	0.01
Maximal dose of cabergoline — mg/wk	0.5±0	0.5±0.2	1	1.6±0.9	1.1±0.6	0.004	1.3±0.4	1.2±0.3	0.19
Average prolactin level at last follow-up visit — μg/liter	44.1±7.0	10.5±4.9	<0.001	48.1±13.1	13.3±4.1	<0.001	54.0±18.4	13.3±4.9	<0.001
Range of follow-up after withdrawal — mo	3–24	24–60	<0.001	3–36	24–60	<0.001	3–30	18–60	<0.001
Median time to recurrence — mo	18	—		12	—		18	—	0.51

* Plus–minus values are means ±SD. P values were calculated with the use of Student's t-test for unpaired (individual) data and the chi-square test or Fisher's exact test for proportions.

(from Colao, 2003)

Although this is a relatively small and selected series, the results of these studies suggest that in patients that have experienced normalization of their prolactin levels, and that do not demonstrate and increase in prolactin with a decrease of cabergoline to a dose of 0.5 mg / week, only ¼ to 1/3 of patients will demonstrate an increase.

Cost

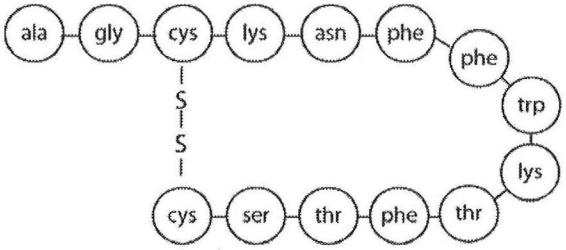
Often, the appearance of a new medication with improved dosing or side effect profiles seems to be synonymous with an increase in pricing structure. Although at first blush this would seem to be so, when taking into account the alteration of dosing, the pricing actually is quite similar.

Drug	Strength	Dose	Cost per unit	Cost per Month	Cost per year
Dostinex	0.5mg	Weekly	$18.99	$75.96	$911.52
Parlodel	2.5mg	TID	$0.84	$75.60	$907.20

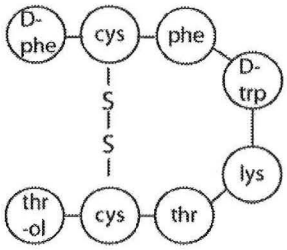
Somatostatin analogues

Somatostatin has long been recognized as a physiological mediator of GH secretion, antagonizing the effects of GHRH. Somatostatin binds to members of the somatostatin receptor family composed of five distinct receptors (sst1-5) within the 7-transmembrane family of G-protein coupled receptors. The effect of somatostatin on GH secretion appears to be mediated at several levels particularly by sst2 and sst5. Of particular importance appears to be the modulation by somatostatin of the activity of inwardly rectifying K+ current. Somatostatin activates this current, resulting in the hyperpolarization of the cell membrane, abolition of action potentials, and a decrease in intracellular calcium concentration. These effects appear to involve the Gαi3 subunit (Takano, 1997). Importantly, these receptors subtypes and inhibitory effectors are also expressed in GH-secreting pituitary tumors (Jaquet, 2000) although heterogeneity has been reported.

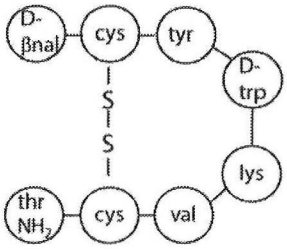
Somatostatin analogues have been developed based on substitutions in the parent somatostatin structure, preserving affinity of binding while improving protein stability. Octreotide (Sandostatin) is a eight residue substituted peptide which binds with high affinity to sst2 and sst5. Although the substitution mutations permitted the development of a clinically useful preparation, the half life was still quite short, requiring two or three daily injections. The formulation of a depot slow release form of this medication has dramatically improved compliance.



Somatostatin-14

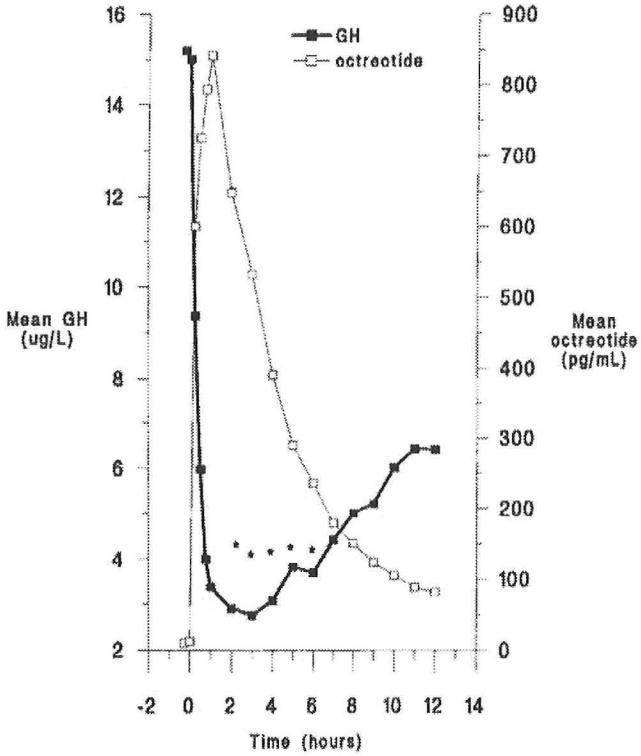


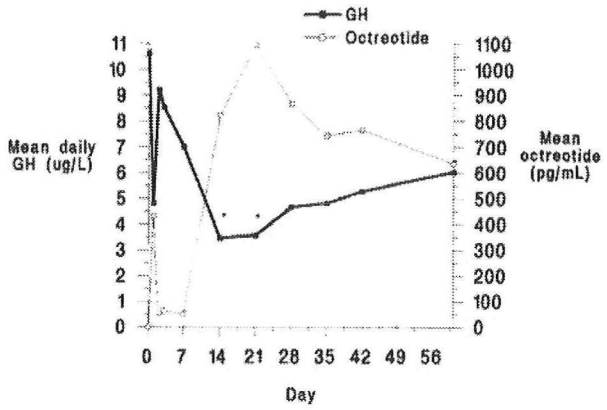
Octreotide



Lanreotide

Structures of Somatostatin-14 and substituted somatostatin derivatives. Octreotide is approved for use in patients with acromegaly in the U.S. Lanreotide has similar properties and has been used in number of trials, particularly in Europe.





The kinetics of release and the biological effects of Sandostatin LAR. The short-term kinetics immediately following initial injection (above), and over the subsequent 60 days (below).

Effectiveness in tumor reduction

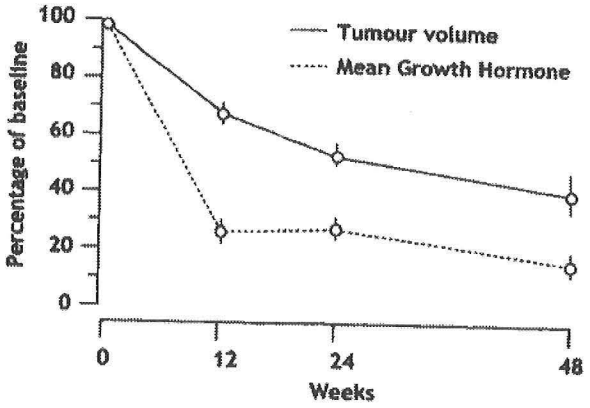
The paradigm that has emerged in recent year is to employ surgery as a first line of therapy for GH-secreting adenomas. As a considerable proportion of patients are left with evidence of hormonal hypersecretion following such surgeries, somatostatin analogues have been employed

alone or in combination with radiation therapy to control such patients. This approach has been promoted, at least in part, by observations indicating that the use of SSA alone was able to effect only modest reductions of tumors size. Further, in many cases, the effects attributable to SSA were difficult to separate from the effects of radiation therapy with which it was often used.

More recently, the use of SSA as primary therapy has been reported. These studies have been relatively small in scope and have been clouded by differences in focus or design. The initial studies of this type were contradictory and employed the subcutaneous formulation of octreotide. The more recently reported series have employed the depot preparation of octreotide

Study	Number of patients	Length of follow-up (Months)	Design	Reduction in tumor size (% of baseline)	Octreotide
Lundin, 1997	11†	70	Pro	51%	SQ
Newman, 1998	13	6	Retro	>25% decrease in only 3 of 13	SQ
Colao, 2001	15	24	Pro	53%	LAR
Bevan, 2002	27 (naïve‡)	12	Pro	50%	SQ, LAR

† These 11 patients were a subset in which the tumor could be discriminated radiographically from the surrounding normal pituitary.
‡ the patients studied in this series were drug-naïve; this may be important as several studies have suggested that response (as assessed by size using MRI) is less – even with normalization of hormonal parameters – in patients that have received prior surgical therapy.



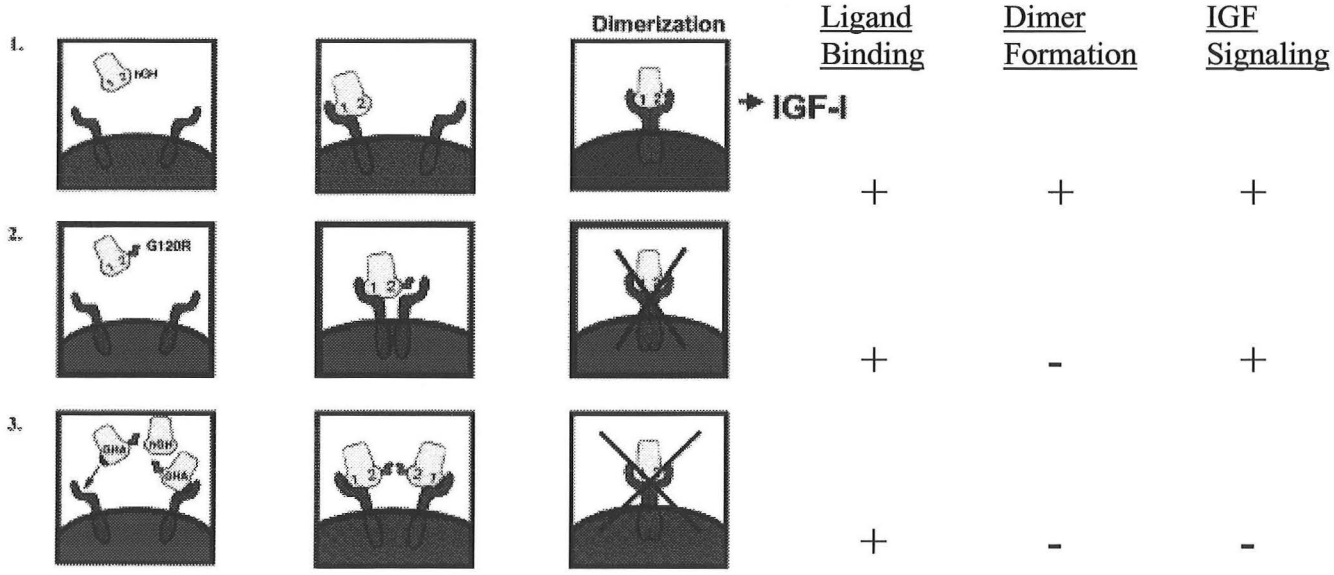
Success rates stratified by pretreatment serum GH concentration

Pretreatment GH level	GH and IGF-I responses	At 24 wk	At 48 wk
<25 mU/liter	Normalized GH (<5 mU/liter)	6/9 (67%)	7/7 (100%)
	Normalized IGF-I	4/9 (44%)	5/7 (71%)
	Normalized GH and IGF-I	2/9 (22%)	5/7 (71%)
25–50 mU/liter	Normalized GH	2/6 (33%)	3/4 (75%)
	Normalized IGF-I	3/6 (50%)	3/5 (60%)
	Normalized GH and IGF-I	2/6 (33%)	2/4 (50%)
>50 mU/liter	Normalized GH	1/9 (11%)	1/3 (33%)
	Normalized IGF-I	1/9 (11%)	0/3 (0%)
	Normalized GH and IGF-I	0/9 (0%)	0/3 (0%)

In aggregate, these studies demonstrate the safety and efficacy of Sandostatin as primary therapy in patients with GH-secreting pituitary tumors. The findings of Lunin, Bevan, and Calao show substantial reductions in tumor size in patients treated win this fashion. No clear-cut explanation has been forwarded to account for the discordant results of Newman. Of note, this latter study employed SQ preparation of Octreotide and the follow-up period was the shortest. Favorable outcomes in these studies appear to be favored in patients with pretreatment GH values of less that 20mcg / L.

Pegvisomant

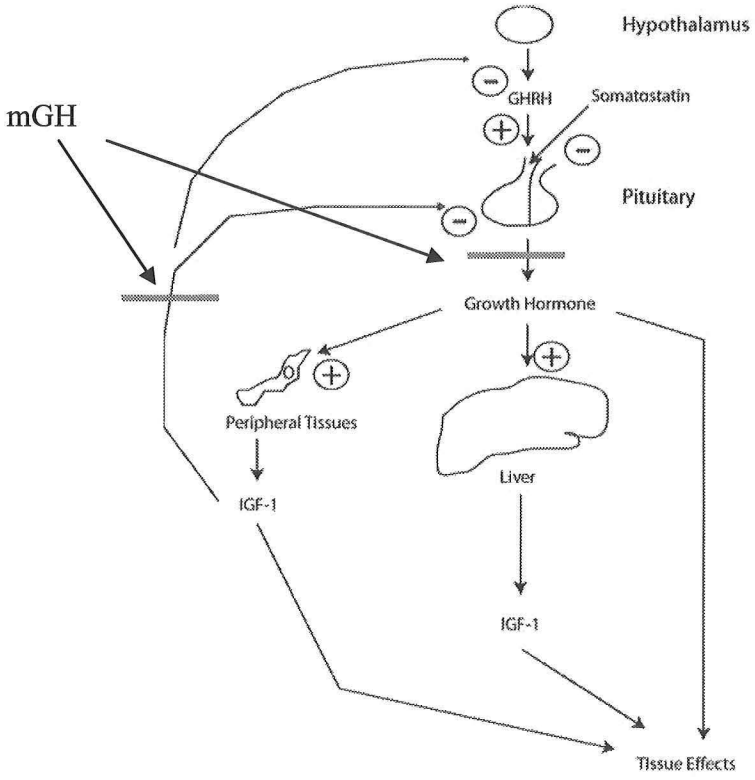
This is the newest therapeutic modality to appear on the scene. This therapy was approved in 2002 for the control of acromegaly. It acts by mechanisms that are completely different from those by which other medical therapies for acromegaly work: acting not to decrease the production of GH by the tumors, but instead acting to interrupt the functional effects that GH mediates peripherally. In order to understand the advantages and challenges that Pegvisomant presents, it is necessary to appreciate how it works.



The normal action of GH in tissues requires the formation of a receptor dimer that initiates the intracellular signaling cascade responsible for effecting the biological events controlled by GH,

such as stimulating IGF-1 production. GH, which contains two distinct binding domains (site I and site II) bind to two GH receptors, resulting in a functional dimeric signaling complex. The formation of this dimeric complex requires the binding of a single GH molecule through these two sites by two GH receptor molecules.

Pegvisomant is a mutant, derivatized GH in which the normal structure and binding properties to the GH receptor have been altered. Beginning with the native human GH structure, eight amino acid substitutions were made in 'site I to enhance site 1 binding to the GH receptor. In addition to these changes, Pegvisomant also contains alterations that serve to antagonize the binding of the mutant molecule via 'site 2'. These changes serve to prevent functional dimerization, reducing the actions of GH (e.g. the production of IGF-1). Additionally the mutant GH is PEGylated to slow its delivery and turnover. It is approved for administration by daily SQ injection.

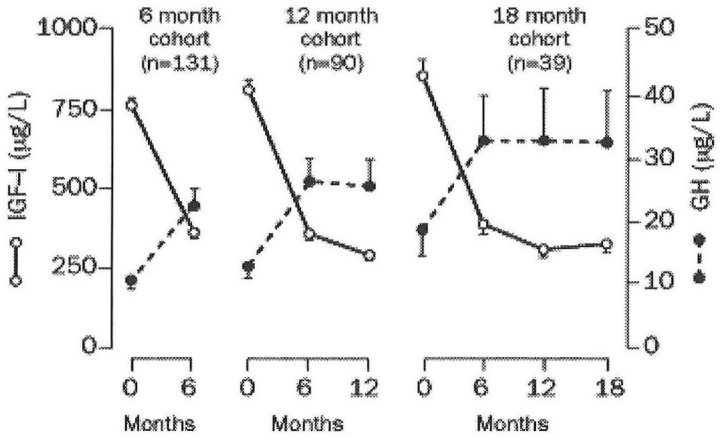


The medication is given daily by daily subcutaneous injection. Its effects of this medication on patient symptoms and biochemical parameters have been examined in a number of different studies . The largest of these trials were reported by van der Lely (van der Lely, 2001). In this study, 160 patients were followed for a period of up to 18 months. Patients all were older 18 years of age and had IGF-1 levels that were at least 1.3 X the upper limit of their age and sex match normal range. Dosing was daily in these studies, beginning at 10 mg /d and titrated in 5mg increments until the IGF I level was normal or to a final maximum dose of 40 mg daily. The design of this study segregated patients into three groups; patients were analyzed according to the length of time that they had received the drug at the 'cut-off' date for data analysis. The characteristics of the three groups were similar (summarized in the table below), the only

differences being the higher average IGF-I and GH in the 18 month cohort – apparently reflecting more severely affected patients entered initially.

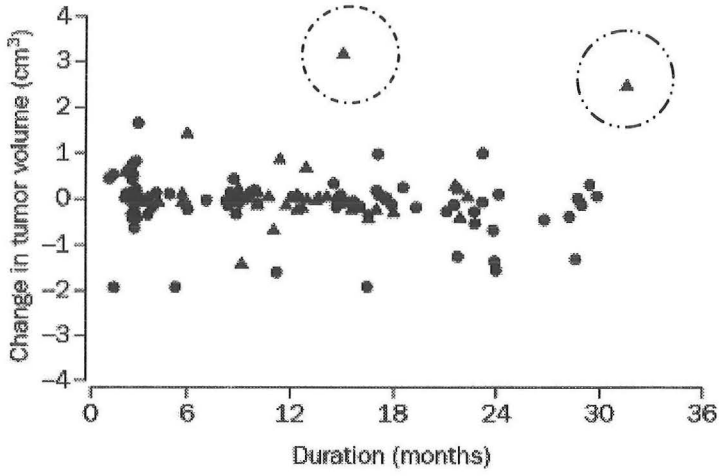
Characteristics	All patients (n=160)	Daily dosing			
		All (n=152)	6 month cohort (n=131)	12 month cohort (n=90)	18 month cohort (n=39)
Age, years†	46±14	46±14	46±14	44±13	42±13
Men	94 (59%)	87 (57%)	75 (57%)	47 (52%)	18 (46%)
Women	66 (41%)	65 (43%)	56 (43%)	43 (48%)	21 (54%)
Duration of disease, years†	8 (8)	8 (8)	8 (8)	8 (7)	8 (8)
Previous therapy					
Surgery	134 (84%)	130 (86%)	111 (85%)	82 (91%)	35 (90%)
Radiation	94 (59%)	89 (56%)	78 (60%)	57 (63%)	26 (67%)
Somatostatin analogue	117 (73%)	112 (74%)	97 (74%)	74 (82%)	33 (85%)
Dopamine agonist	76 (48%)	73 (48%)	67 (51%)	48 (53%)	19 (48%)
Bodyweight, kg†	94 (21)	94 (21)	94 (21)	93 (20)	92 (19)
Growth hormone, µg/L†	10·2 (16·0)	10·4 (16·3)	10·9 (17·0)	13·2 (19·7)	19·2 (27·0)
IGF-1 µg/L†	762 (330)	755 (327)	760 (306)	806 (297)	847 (321)
Pituitary tumour volume, cm^3†	2·39 (3·45)	2·36 (3·48)	2·14 (2·47)	2·44 (2·70)	2·49 (2·58)

†Values are means (SD).



The administration of Pegvisomant to patients led to a marked decline in IGF levels. In patients treated for 12 or more months, 87/90 normalized their IGF-I levels. As shown above, serum GH levels rose in each cohort during treatment. Though not directly examined in this study, prior investigations had demonstrated that these biochemical effects were associated with marked improvements in scores assessing acromegalic symptoms (Trainer, 2000). In this cohort of patients, most side effects were limited to local reactions at the injection site. Two patients had increases of alanine and aspartate aminotranferases, and were withdrawn from the study.

A very important consideration in these studies was the concern that changes in IGF-I effected in this fashion might tend to augment tumor growth, owing the removal of IGF-I feedback inhibition. For this reason, tumor size was carefully assessed before and during the treatment period (see figure below). It is evident from an inspection of this data that in the vast majority of patients treated, no change in tumor size occurred. Overall, in 78patients previously treated with radiation therapy, the tumor size decreased slightly. In 53 patients who had not been treated with radiation, a small increase in tumor volume was reported. Two patients demonstrated enlargement to the point of requiring surgical intervention.



A major consideration of any new therapy is the cost, compared to existing therapies. A summary of the costs of these different therapies is depicted in the table below. For the purposes of comparison only, if one assumes that the control effected is equal between starting doses of the different agents, the cost of Sandostatin LAR is approximately 3-4 times that of SQ Sandostatin; the cost of the lowest dose of Somavert is ~ 10 X that of the initial dose of SQ Sandostatin.

Drug	Strength	Dose	Cost per unit	Cost per Month	Cost per year
Sandostatin	50 mcg	TID	$2.87	$258.30	$3,099.60
Sandostatin LAR	10mg	Monthly	$997.45	$997.45	$11,969.40
Sandostatin LAR	20mg	Monthly	$965.90	$965.90	$11,590.80
Sandostatin LAR	30mg	Monthly	$1,467.41	$1,467.41	$17,608.92
Somavert	10mg	Daily	$90.00	$2,700.00	$32,400.00
Somavert	15mg	Daily	$135.00	$4,050.00	$48,600.00
Somavert	20mg	Daily	$180.00	$5,400.00	$64,800.00

Postoperative management and follow up of patients with pituitary tumors

The post operative evaluation and follow-up of patients differs for all patients entail common elements. In patients in whom surgery has been performed, assessments of residual pituitary function should be conducted to determine whether deficits have been corrected or have resulted from the surgery. Of particular attention is attention to the adrenal (most easily assessed initially by measurement of an 8AM cortisol) and thyroid hormone axes (measuring fT4 or T4, not TSH). In patients whose subsequent course suggests GH deficiency, formal testing to identify GH deficiency is indicated. It should be recognized that patients at highest risk for the development of these deficiencies are those that have received combinations of surgery and radiotherapy (Boelaert et al, 2001, and references within).

The follow-up of patients with acromegaly presents specific problems, as continued excess growth hormone secretion has been associated with increased mortality (Orme, 1998, Beauregard, 2003).

Much of the controversy has related to the levels that should be accepted as indicative of cure. Recent studies have suggested that progressively lower definitions of cure may be appropriate (Serri, 2004).

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