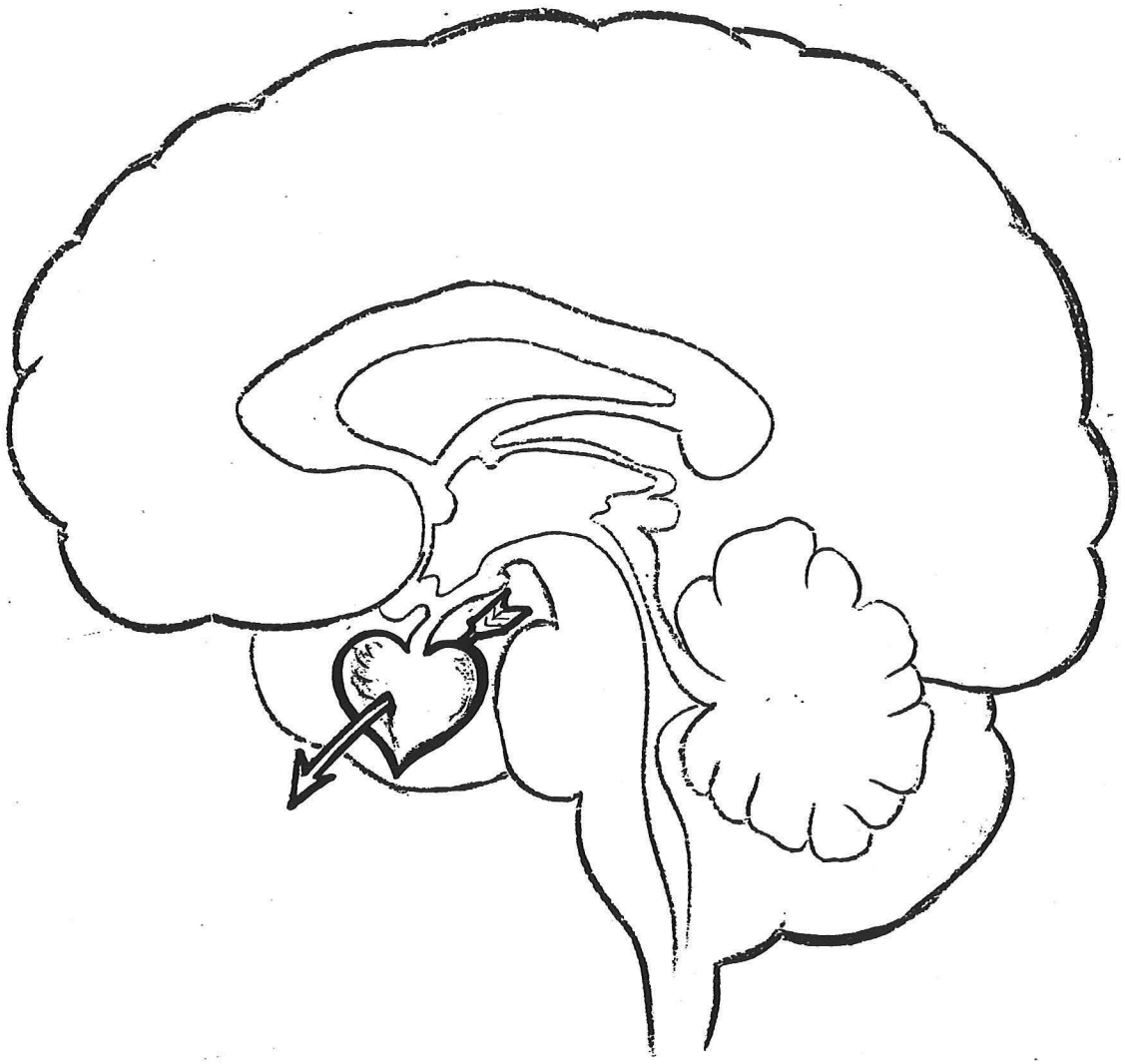
Management of Pituitary Adenomas



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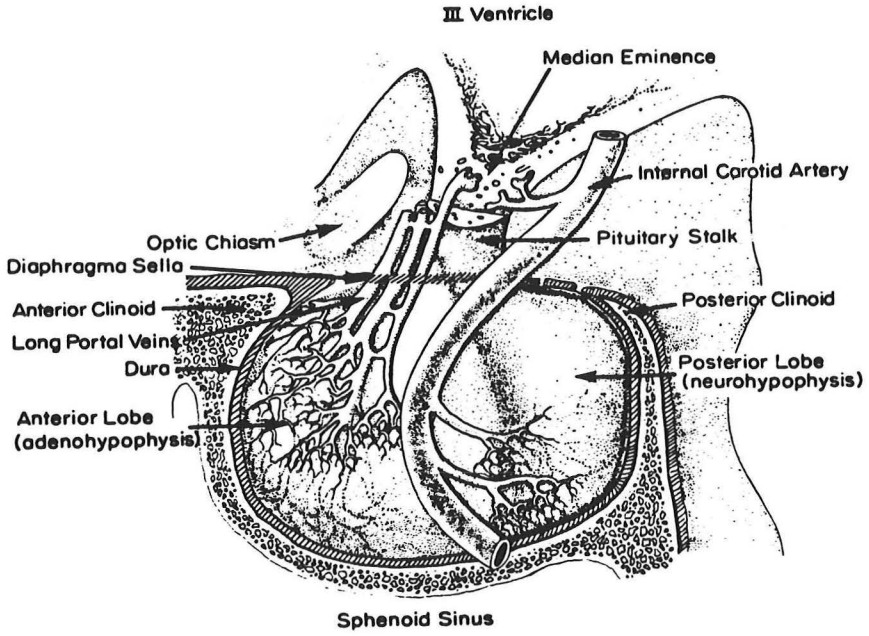


FIGURE 1. Schematic representation of the human pituitary gland in relation to its surrounding structures. Refer to text for detailed description.

The pituitary gland controls a number of important metabolic processes. The anterior pituitary regulates the normal function of the thyroid, adrenal glands, and the gonads via the elaboration of a group of glycoprotein hormones. The posterior pituitary controls serum osmolality by regulating the secretion of antidiuretic hormone. Just as the cells of the anterior pituitary control the function of the hormone producing endocrine organs, they themselves are controlled by centers within the hypothalamus. Thus, groups of neurons within the hypothalamus secrete specific trophic factors which are carried to the anterior pituitary by the portal vessels and that stimulate the secretion of the hormones from the pituitary (1). The notable exception to this interplay of positive regulatory factors on the anterior pituitary is the control of prolactin secretion which, for the most part, is under tonic negative regulation exerted by dopaminergic neurons (2).

TABLE I

Cell Type	Hormone (properties)	Size	Comments
Corticotropes	Adrenocorticotropin (ACTH)	39 amino acids	(Also synthesize α MSH, β lipotropin and β endorphin from a single precursor)
Somatotropes	Growth Hormone (GH)	191 amino acids	
Mammotropes	Prolactin (PRL)	198 amino acids	
Thyrotropes	Thyrotropin (TSH)	α subunit: 89 β subunit: 112	- TSH, FSH, & LH share a common α subunit
Gonadotropes	Luteinizing Hormone (LH)	α subunit: 89 β subunit: 115	- LH and FSH are produced by the same cells
	Follicle-stimulating Hormone (FSH)	α subunit: 89 β subunit: 115	- LH and FSH are produced by the same cells

Six well defined polypeptide hormones are secreted by 5 distinctive cell types, as defined by immunochemical criteria (see Table I). Each of these cell types is characterized by the type of glycoprotein hormone or hormones that it synthesizes and secretes: somatrophs (GH), lactotrophs (PRL), thyrotrophs (TSH), gonadotrophs (FSH and LH) and corticotrophs (ACTH). The only exception to the one cell-one hormone rule is the gonadotroph, which has been shown to synthesize both LH and FSH. As indicated, these hormones fall into three categories - the members of the ACTH and GH hormone family are single polypeptide chains. By contrast, LH, FSH, and TSH are composed of two distinctive units - an α subunit that is common to all three hormones and a distinctive β chain that is unique to each hormone.

TABLE II

Representative Classification of Pituitary Tumors
(Adapted from Ref. 3, ca 1966)

Type	% of Total	Evidence of Hormone Hypersecretion
Chromophobe Adenomas	70	No
Acidophilic Adenomas	20	Acromegaly
Basophilic Adenomas	rare	Cushings

The classification of pituitary adenomas that are derived from these cell types has evolved with time and has taken several forms. As recently as 1966 (3), the classification of pituitary adenomas was not complex. 20% of tumors were found to be acidophilic on hematoxylin/eosin stains. It was recognized quite early that this tumor type was associated with 'gigantism' when it occurred prior to epiphyseal fusion and acromegaly when present in patients following epiphyseal fusion. A small percentage of tumors were shown to have basophilic staining patterns and were associated with Cushing's disease. The remainder - 70%-80% of pituitary tumors were 'chromophobic' - that is, they did not take up significant stain on H&E stains. At this time, such tumors were not clearly associated with known syndromes caused by hormone hypersecretion.

The availability of assays to measure or detect the pituitary hormones has radically altered the classification of pituitary adenomas. First, it has extended the definition of the classic syndromes ascribed to pituitary hormone hypersecretion. Thus, allowing the identification of patients with physiologically important elevations of GH or ACTH even prior to the establishment of the full blown syndrome. As a result, the terms acromegaly and

syndrome. Table III includes this expanded definition and the tests employed to establish these diagnoses.

TABLE III-A

CLASSIC SYNDROMES OF PITUITARY HORMONE HYPERSECRETION

	Symptoms	Diagnostic Tests	Caveats	Approximate Frequency ATT	Macroadenomas (14)
Cushing's Disease	Obesity Plethora Hirsutism Menstrual Irregularity	1) Overnight dexamethasone suppression test and 24 h urinary free cortisol (4, 5) 2) Low/high dose dexamethasone suppression test (4, 5) 3) CT/MRI of head and abdomen 4) Petrosal sinus sampling (6,7)	1) Hyperfunctioning adrenal adenoma 2) Ectopic ACTH production	5%	unusual
Acromegaly	Soft tissue growth (hands, feet, face) Hirsutism Sweating Bony changes (mandible tufting of planges) Peripheral neuropathy Visoeromegaly	1) GH level, random and 60 min after 50 g glucose load (8) 2) Somatomedin C level (9)	1) Ectopic GH or GHRH secretion	10%	15%

TABLE III-B

OTHER CLINICAL PATTERNS OBSERVED IN PATIENTS WITH PITUITARY ADNOMAS

	Symptoms	Diagnostic Tests	Caveats	Approximate Frequency ATT	Macroadenomas (14)
Hyperprolactinemia	Galactorrhea Menstrual irregularities (female) (10-12) Hypogonadism visual abnormalities in men (13)	1) Serum prolactin	1) Pharmacologic and endocrinologic causes of increased prolactin (14)	70%	30%
Gonadotroph Cell Adenomas (14a)	Middle aged men Visual field abnormalities Normal gonadal Function	1) Serum FSH, LH, α subunit measurements, testosterone	1) α subunit levels may be elevated with other tumor types (e.g., acromegaly) (15)	5%	
			FSH		17%
			α subunit		7%
			non	10%	40%
Non-Functioning Adenomas	Usually large at presentation with supra-extrasellar extension		1) May show hormone secretion or hormone gene expression using in vitro cultures or tumor immunohistochemistry (16-21)		
TSH-Secreting Adenomas (10a)	Hyperthyroidism evident	1) TSH measurement 2) Thyroid functions	1) Separate from primary hypothyroidism and thyroid hormone resistance (23) 2) Generalized or pituitary thyroid hormone resistance	0.2%	

In addition to the well defined entities of Cushing's and acromegaly, the availability of antibodies specific for the distinctive pituitary hormones has permitted the definition of previously unrecognized syndromes. The first of these was that associated with hyperprolactinemia. Prior to the availability of assays for prolactin, the majority of pituitary adenomas were recognized as chromophobic and were believed to be endocrinologically silent. Subsequent to the availability of these antibodies, it was recognized that women with a variety of syndromes characterized by amenorrhea and galactorrhea were in fact due to hyperprolactinemia caused by prolactin-secreting pituitary tumors (10). In one representative series, most patients with prolactin-secreting pituitary tumors had both galactorrhea and amenorrhea (59/73) while nine had amenorrhea alone (9/73) and only one had galactorrhea and normal menses (11). In some series, as many as 15-20% of patients with secondary amenorrhea had microadenomas and hyperprolactinemia (12). In men, prolactin-secreting tumors are associated with hypogonadism and less frequently with galactorrhea (13). Because subtle gonadal dysfunction is not usually as obvious in men, the prolactin-secreting tumors are usually larger at presentation in men.

The availability of hormone assays for the gonadotropins permitted the recognition of a fourth major category of pituitary adenoma. Beginning in the mid 1970's, isolated cases were reported that described patients with macroadenomas and visual abnormalities that secreted FSH or LH or both. Subsequently, this category of patients has been increasingly recognized. In one series of 139 male patients with pituitary adenoma (14a), 17% were shown to represent gonadotroph cell adenomas. Clinically, most of the patients of this type were men with a history of normal sexual function that presented with visual impairment. It is likely that this series is not completely representative, as it included only men, and a high percentage of these patients were referred for visual abnormalities (i.e., large tumors). Biochemically, this type of tumor is heterogenous, with some tumors secreting intact FSH, others intact LH, and still others secreting free α or β subunits. The results of these and other (15) series demonstrate that the frequency with which this entity occurs may not be as low as has been suggested previously. Furthermore, the identification of these secretory products is of more than academic interest. First, these hormone measurements may be crucial to distinguishing a pituitary adenoma from other non-adenomatous lesions, such as meningiomas and craniopharyngiomas which may require substantially different therapy. Second, these measurements can serve as tumor markers that permit an assessment of the response to therapy.

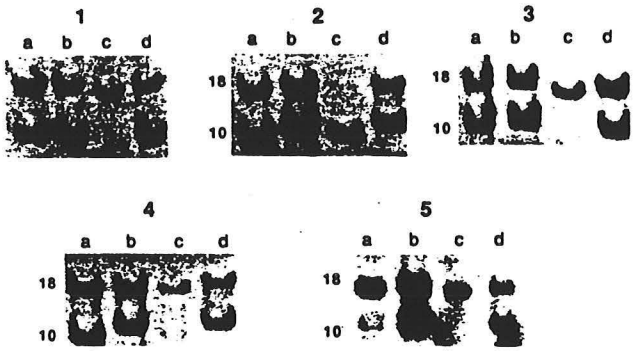
The category of 'non-functioning' adenomas has gotten increasingly smaller over the last twenty years and may get smaller yet as new assays are developed. It is interesting to note that when samples from clinically non-functioning tumors are studied histologically or <u>in vitro</u>, a significant number of "nonfunctioning" pituitary adenomas can be shown to synthesize and/or secrete intact hormone or α subunit (16-21).

TSH-secreting tumors that are hormonally active clinically are quite rare. In the surgical experience of one renowned neurosurgeon (22), two cases out of 1000 pituitary adenomas were believed to be TSH-secreting tumors. Histochemical studies (18), however, indicate that this tumor type may be more frequent than is recognized clinically. The only important diagnostic decision is to identify those patients with primary hypothyroidism, a simple exercise with

currently available tests. A more difficult task is presented by patients with pituitary or generalized resistance to thyroid hormone (23).

Pathogenesis

The realization that the growth and function of the pituitary is under regulatory control by the hypothalamus, led to the suggestion that pituitary tumors might in fact be caused by abnormal trophic influences from higher centers within the brain. The recognition that patients with primary gonadal or thyroid failure could present with significant pituitary enlargement/hyperplasia tended to reinforce this concept (24-26).



Clonal analysis of pituitary tumors at the HPRT gene. Southern blots of DNA from blood leukocytes (lanes *a* and *b*) and nonfunctioning pituitary tumors (lanes *c* and *d*) from patients 1–5. Lanes *a* and *c*, 7.5 μg of leukocyte genomic DNA restricted with Bam H1, Pvu II, and Hpa II; lanes *b* and *d*, 7.5 μg of leukocyte genomic DNA restricted with Bam H1 and Pvu II alone. 18 and 10 are the lengths in kilobases of the two HPRT alleles.

Figure 2

Recently, however, two lines of evidence have appeared that suggest that such a "regulatory" scenario is unlikely. The first pertains to the clonality of pituitary tumors. If uncontrolled trophic influences alone were responsible for the appearance of pituitary tumors, then one would expect that such tumors would be polyclonal in origin - that is, derived from many different cells. By contrast, if a somatic mutation (in an oncogene, for example) is responsible for the appearance of a tumor then each of the tumor cells should be monoclonal (that is derived from a single cell) and have the same genetic composition. Two recent publications have appeared which address this issue (27, 28). In both papers, the authors have employed the technique of Southern analysis to examine genes on the X-chromosomes of female patients with pituitary tumors. This strategy was employed because in women only a single X-chromosome is active and the other is not active. "Inactivation" of one of the X-chromosomes occurs randomly in each cell of the body. Since certain restriction enzymes are able to distinguish genes that are active and inactive, this technique can be used to examine whether the cells of a tumor are derived from one cell ("monoclonal") and thus showing that only one gene copy is inactive or more than one cell ("polyclonal") suggest derivation from more than one cell. Thus, when this analysis is performed on blood leukocytes (containing a mixture of cells that have randomly inactivated one chromosome or the other), fragments derived from

both the inactive and active gene are detected with equal frequency. By contrast, when DNA samples were analyzed that were obtained from several non-functioning pituitary tumors (28), a different pattern was frequently detected which indicated that in all of the cells only one or the other X chromosome had been inactivated. The results of these studies are similar to those reported by Herman et al (27) which examined samples from GH, prolactin, and ACTH secreting tumors. The results of these studies indicate that the majority of pituitary tumors are monoclonal in origin and support the theories that have postulated that somatic mutations underlie the genesis of pituitary adenomas.

TABLE IV

α_s Mutations in human pituitary tumours

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

Eight pituitary tumours are divided into groups 1 and 2 by adenylyl cyclase activities. Columns on right list, for each tumour, the source of DNA (genomic DNA from tumour, cDNA from tumour, or genomic DNA from peripheral blood of the same patient) and the amino acid(s) encoded by codons 201 and 227, determined by sequencing PCR-amplified cDNA or genomic DNA. Two amino acids are listed when bases encoding both were found in a single DNA sample. Numbers in parentheses indicate the number of individual M13 cDNA clones sequenced that encoded the specified amino acid. Pituitary adenomas from patients with GH excess were surgically removed and stored at −70 °C. To measure adenylyl cyclase activity, membranes were prepared from tumour homogenates and adenylyl cyclase activities measured[8] in the absence or presence of 10 mM NaF. To perform sequence analysis of subcloned PCR amplified cDNA, total RNA was extracted from tumour homogenates as described[36]. First strand cDNA was produced in a reaction containing 7 μg total RNA, oligo(dT) primer and reverse transcriptase, according to the protocol in the AMV reverse transcriptase kit from Bethesda Research Laboratories. Four per cent of the cDNA reaction volume was amplified as described[12]. Primers were designed to match the 5′ and 3′ noncoding regions of human α_s (ref. 37), in order to amplify the complete coding region. Each primer contained an artificial restriction site at its 5′ end to facilitate subcloning. The 5′ primer (5′-GCCGGTACCCGGCCGCGCCCCGCCGCCGCCG-3′) had a *Kpn*I restriction site and the 3′ primer (5′-TTAAAGCTTTAATTAAATTTGGGGGTTCC-3′) had a *Hind*III restriction site. The PCR mixture contained 2.5 U DNA polymerase from *Thermus aquaticus* (Perkin-Elmer Cetus) and 25 pmol of each primer. Amplification was accomplished in 40 cycles of 1 min at 94 °C, 1 min at 58 °C, and 2 min at 72 °C, in a Perkin-Elmer Cetus Thermocycler. Amplified DNA was desalted and primers were removed by gel filtration with G-50 Sephadex spin columns (Boehringer Mannheim) and ethanol precipitation. The purified DNA was digested with *Kpn*I and *Hind*III and subcloned into M13mp18 or M13mp19. The Sequenase method of dideoxy sequencing was used to determine the entire α_s coding sequence from at least two M13 clones derived from two separate amplification reactions for each group 2 tumour. For direct sequence analysis of PCR amplified cDNA and genomic DNA, first strand cDNA from tumours was prepared as described above. Genomic DNA was extracted from tumours or peripheral blood by homogenizing samples in a glass-Teflon homogenizer in a lysis buffer (4 M Urea, 1% Triton X-100, 10 mM EDTA, 100 mM NaCl, 10 mM Tris, pH 8.0, 10 mM DTT, and 0.2 mg ml^{-1} Proteinase K); samples were incubated overnight, repeatedly extracted with phenol/chloroform, and DNA recovered by ethanol precipitation. PCR amplification was performed with primers flanking a region that encompassed both codons 201 and 227; the 5′ primer (5′-GTGATCAAGCAGGCTGACTATGTG-3′) was located in exon 7 and the 3′ primer (5′-GCTGCTGGCCACCACGAAGATGAT-3′) was located in exon 10 (ref. 37). Four per cent of the cDNA reaction volume or 50 ng genomic DNA was amplified as described above, except that unequal molar concentrations (12.5 pmol:1 pmol) of the primers were used to generate single-stranded DNA for direct sequence analysis, as described[38]. The reaction mixture was desalted and excess dNTPs were removed by repeated (3–4×) spin-dialysis on a Centricon 30 (Amicon). Samples were then vacuum-dried and resuspended in water. Half of the reaction product was sequenced using Sequenase. The primer used at low concentration in the amplification reaction was used in the sequencing reaction.

A clue to the nature of these mutations has come from a study of GH secreting adenomas. Remember that the stimuli to secretion also will stimulate hyperplasia of the cells of the pituitary. In the case of the somatotrope, GHRH binds to a surface receptor which stimulates an intracellular response that includes cellular proliferation and the secretion of growth hormone. It has been suggested that this response to GHRH is coupled through regulatory G-proteins to the production of intracellular second-messengers, such as cyclic AMP (29, 30). In 1987 a very interesting paper appeared (31) that demonstrated human GH-secreting adenomas, one group which contained increased basal levels of adenylate cyclase and abnormal Gs activity. Subsequent reports have confirmed that such findings are consistent and have identified two types of mutations that appear repetitively in a subset of GH secreting pituitary tumors (32). Introduction of these mutations into normal cDNAs encoding Gs have confirmed that these mutations are likely causally linked to the abnormal cellular growth and function that is observed. These findings also demonstrate that these mutations cannot even explain the genesis of all types of GH secreting pituitary tumors. It seems likely, however, that other types of somatic mutations affecting the signalling/coupling mechanism may well be involved in the genesis of GH secreting and other types of pituitary adenomas. Interestingly, this molecular heterogeneity is also correlated with differences in the clinical behavior of tumors bearing these mutations (33, 34).

THERAPY

Definitive therapy of a pituitary tumor depends on several factors: 1) the size of the tumor, 2) the degree of invasiveness/extension, and 3) the cell type of the tumor. Often, a single approach is not adequate, and control of tumor will require a combination of surgery and radiation therapy and, in some cases, may directly involve medical control.

Neurosurgery

Neurosurgical removal or debulking is the principal method that is employed as therapy in the treatment of many types of pituitary tumor. With the exception of prolactinomas (see below), surgical removal of the tumor is the treatment of choice - the only exceptions being those patients that are not good surgical risks. In these patients radiation therapy is often the therapy of choice.

Two principal types of surgical approaches are employed. Historically, the first widely employed method was the transfrontal approach. This technique employed craniotomy and was associated with a significant incidence of morbidity and neurological sequelae. This approach is not widely employed and is currently reserved for cases in which the extent of pituitary tumor invasion requires a wider surgical field. Most pituitary tumors (>90%) are currently removed using a transsphenoidal approach. This technique carries with it a much lower incidence of complications. In one large series of 1000 patients, only two operative deaths occurred (0.2%) (22).

The results of neurosurgical therapy depends in large part on how success is defined. Pituitary adenomas that are not associated with hormone hypersecretion are usually large mass lesions and the results of neurosurgery can only be defined in terms of debulking and/or decompression of the tumor. These goals

are limited and while nearly always accomplished are usually combined with other forms of therapy (e.g., radiotherapy) to prevent or slow tumor regrowth.

In patients that manifest clinical or biochemical evidence of hormone hypersecretion, additional methods are available to assess the adequacy of intervention, and the degree of success can be much more precisely defined. Thus, in surgical series of prolactinoma, in those series where postoperative prolactin measurements have been assessed, a large percentage recurs. For example, Parl et al (35) reported that even when postoperative prolactin measurements are normal, these gains are often not permanent. In this series, 24 female patients were followed for a mean of 62 months following transspehnoidal (22/24) or transfrontal (2/24) resection. In this group, the recurrence rate was 31% for microadenomas and 91% for macroadenomas. This experience is general and similar results have been reported by numerous other investigators. When all of the aforementioned series using values from a number of such series (totaling nearly 300 patients) in which followup prolactin values and recurrence rates are provided (summarized in Ref. 36), at least ≃14% of microadenomas and ~30% of macroadenomas will recur within 5 years. While this wholesale summation of multiple series should be carefully interpreted, these results demonstrate the high recurrence rate of such tumors approached surgically when adjunctive measures are not employed.

TABLE V

RESULTS OF TRANSSPEHNOIDAL SURGERY IN PATIENTS WITH ACROMEGALY

Reference	Number of Patients	Micro/Macroadenomas	Postoperative GH <5; GS <2.5[a]	Followup (yrs) <5; GS <2.5[a]
(37)	214	-	116/214	131/165
(38)	25	8 micro 17 macro	8/8; 8/8 14/17; 13/17	8/8; 7/8 (1-6 yrs) 11/17; 11/17
(39)	25	9 micro 16 macro	6/9; 6/9 8/16; 8/16	all 14 still 'cured', 1.5-5.5 yrs followup

[a]GS <2.5 = glucose suppressed GH <2.5 ng/ml

The results of series reporting the surgical treatment of acromegaly, while similar, are even more difficult to interpret. This is owing to the fact that criteria used to define a 'cure' varies from series to series. Furthermore, it is clear that isolated measurements of growth hormone are often not reliable indicators of disease activity in acromegaly. In one large recent series (37) 56% of patients were found to have postoperative GH measurements less than 5 ng/ml and 78% <10 ng/ml. These same authors have compiled the results of 30 other series containing 1360 cases. Assuming that postoperative growth hormone measurements were obtained in like manner in all, postoperative growth hormone values of <5 ng/ml were obtained in 60% of patients and values of <10 ng/ml were

obtained in 74%. However, the variations in serum GH that occur even in acromegalic subjects make the interpretation of the incidence of such "cures" reported in this and other neurosurgical series difficult to interpret. Some investigators have suggested that the most common definition of 'cure' (postoperative GH levels of <5 or <10 ng/dl) may be inadequate criteria for assessing cure. While such measurements may be helpful in focusing attention on those patients likely to require further therapy, they are not necessarily synonymous with cure. However, in more recent studies (38, 39) the combination of postoperative growth hormone levels (<5 ng/ml) and a suppressed growth hormone measurement (<2.5) had a high predictive value of 'normalization' of growth hormone secretion (Table IV). Notably, other studies in which patients believed to be "cured" postoperatively were found to have abnormal GH dynamics when more detailed endocrine evaluations were performed (40, 41). Taken together, these studies suggest that substantial normalization of GH dynamics resulting from neurosurgical intervention alone may be possible in over 50% of patients. This appears to be most consistently true for microadenomas. These studies suggest that if basal fasting GH measurements and glucose suppressed growth hormone measurements are normal, that a large percentage of these patients will continue to have 'normal' GH levels at long intervals postoperatively. As noted, most of these followups are relatively short (average of 6 and 3.5 years) and have employed methods that may overestimate the extent of normalization of growth hormone secretion.

Prolactinomas and growth hormone secreting pituitary tumors together account for 75% or more of pituitary adenomas. The results of neurosurgical intervention in other tumor types (FSH, LH, α subunit, TSH-secreting tumors) is similar to that reported for prolactinomas and GH secreting tumors, particularly when it is taken into account that FSH, LH, α subunit, or "nonsecreting" tumors are more often large at presentation. The only tumor type that presents a different pattern is the pituitary adenomas that secrete ACTH. This is because the tumors associated with Cushing's disease are generally quite small. In fact, even in patients with classic abnormalities of cortisol and ACTH secretion, pituitary adenomas cannot be detected by CT in 70% of patients (42) and cannot be detected in 50-60% of patients even using gadolinium enhanced MRI scans. Despite this failure to demonstrate the tumor preoperatively, 90% of patients that show classic biochemical profiles have a pituitary adenomas at the time of exploration. Thus, in the majority of cases, the important consideration is to establish the diagnosis of pituitary Cushing's disease unambiguously, employing the methods referred to above (4-7). In those patients with microadenomas, good success rates can be expected - the high success rate is probably related to the smaller tumor sizes at diagnosis and not to intrinsic differences in the biological behavior of the tumor (43-46).

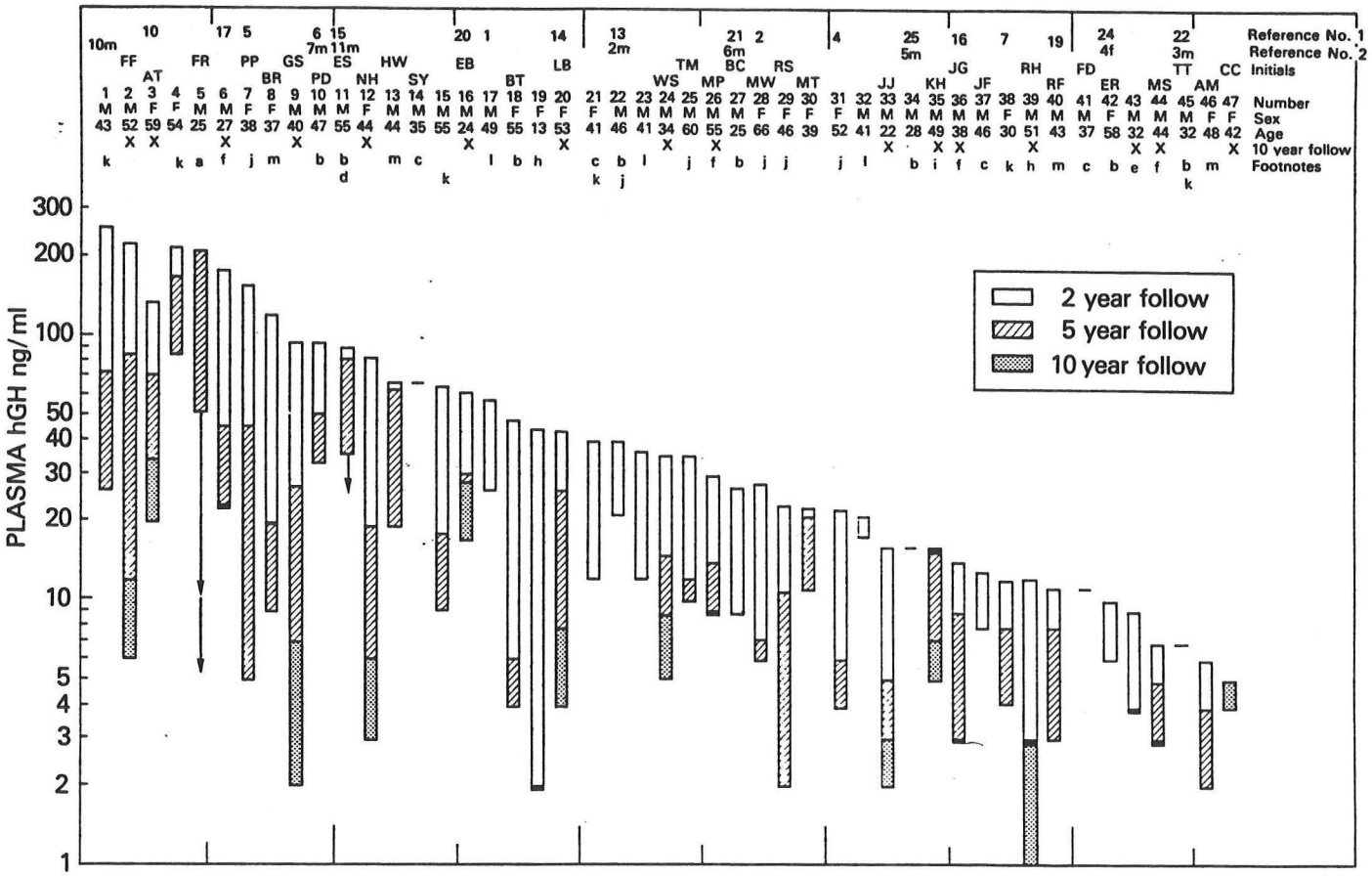
SUMMARY

Neurosurgical therapy is an effective form of therapy for almost all types of pituitary adenomas. It is most effective when used as therapy of small tumors but can be effective in large tumors as well, particularly when used in combination with other forms of therapy.

Radiation Therapy

In most cases, the literature pertaining to radiation therapy of pituitary tumors is intertwined with that of the neurosurgical and medical management of

pituitary adenomas. Early protocols of radiotherapy were characterized by substantial morbidity rates, including optic nerve or chiasm damage, brain necrosis, and carcinogenesis. These complications appear to be minimized by current protocols which employ a cummulative dose of 45 gy or less.



Plasma GH before treatment and at intervals after therapy in patients referred for therapy with conventional supervoltage irradiation. The top of each bar is the plasma GH (in nanograms per ml) before treatment. Patients were evaluated at 2, 5, and 10 yr after radiotherapy and the plasma GH was plotted. □, Lower line represents the GH at 2 yr after treatment; ▭, lower line represents the value at 5 yr; ▭, lower line represents the value at 10 yr. Only a single value is shown for patients who were lost or died before the 2-yr follow-up interval. ■, No fall in GH occurred in the subsequent interval. Along the top of the figure are the initials and numbers used to identify the patients in our previous publications [Ref. 1 refers to McGuffin *et al.*, 1974 (25), and Ref. 2 refers to Sober *et al.*, 1974 (29)], the number assigned to each patient in this paper (from 1–47), the age at the time of treatment; and the sex of the patient. Patients followed for 10 yr are identified by X. Other notations in the heading are: a) the first arrow indicates the fall in GH immediately after hypophysectomy; the second arrow is the fall in GH 3 yr after hypophysectomy; b) Patients who died after the last follow-up indicated; c) patients lost to follow-up after the last follow-up indicated; d) the arrow indicates the GH value 6 months after hypophysectomy; e) no change in GH between 2 and 10 yr after therapy; f) no change in GH between 5 and 10 yr after therapy; h) no change in GH between 2 and 5 yr after therapy; and i) no change in GH between pretreatment and 2 yr after therapy. Patient 6 was M.M. in Ref. 15, M.C. in Fig. 2, and J.M. in Fig. 3 in Ref. 16. Patient 19 is reported in detail in Ref. 30. Patient 31 was M.E. in Ref. 15 and M.M. in Ref. 16. Patient 34 was B.M. in Ref. 15. Patient 43 was B.M. in Refs. 15 and 16.

The following notations indicate the methods used to irradiate the pituitary tumor (see Ref. 15 for methods reported previously): j) 4000–4600 rads, maximum 200 rads per day, two or three fields (360° rotation in case 54 only), 2 million electron volts Van de Graff (15); k) 4000–5000 rads, maximum 200 rads per day (5600 rads in case 21 only), two or three fields, cobalt; l) 5000 rads, maximum 200 rads per day; two or three fields; 6 million electron volts Lineac; m) 4000–5000 rads, treated at other institutions, exact records not available.

Figure 3

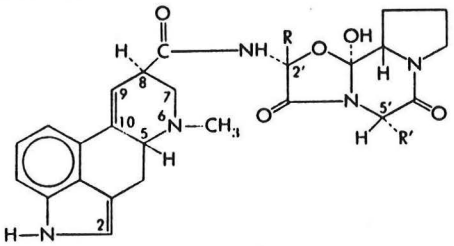
When administered as a single agent in such doses radiotherapy is well tolerated. The principal drawback to such an approach is the long period before

radiation has an effect. This graph is taken from a report detailing the results of 16 patients with acromegaly (47). These results indicate that radiotherapy can effectively control GH hypersecretion, and similar series have been reported for other pituitry tumor types (48, 49). This report also illustrates the major disadvantage of radiotherapy - as employed as a single agent - that is, its slow onset of action. Thus, while control of hormonal hypersecretion is eventually achieved in a high percentage of patients, this change does not occur rapidly and may take several years to achieve. The doses of radiation employed has been progressively lowered. Recent work suggests that adequate responses may be obtained at radiation doses substantially lower than that currently employed (49a). As such, radiotherapy is not employed as initial therapy except in cases where surgery is contraindicated or in cases where medical therapy is not effective. It is, however, particularly effective when employed in combination with surgical or medical therapy.

Medical Therapy

The broad based basic research effort that led to the definition of the major pituitary and hypothalamic hormones has led as well to important advances in the medical management of pituitary tumors. These developments center on two classes of compounds: 1) the ergot alkaloids, such as bromocriptine, and 2) the somatostatin analogues.

B. AMINO ACID ALKALOIDS



ALKALOID §	R(2')	R'(5')
Ergotamine	$-CH_3$	$-CH_2-$phenyl
Ergosine	$-CH_3$	$-CH_2CH(CH_3)_2$
Ergostine	$-CH_2CH_3$	$-CH_2-$phenyl
Ergotoxine group:		
Ergocornine	$-CH(CH_3)_2$	$-CH(CH_3)_2$
Ergocristine	$-CH(CH_3)_2$	$-CH_2-$phenyl
α-Ergocryptine	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
β-Ergocryptine	$-CH(CH_3)_2$	$-CH(CH_3)CH_2CH_3$
Bromocriptine ¶	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$

Figure 4

Bromocriptine is one of a class of compounds (also including lisuride and pergolide) that are ergot derivatives and that directly stimulate dopaminergic receptors. As prolactin secretion is inhibited by dopaminergic stimulation, such compounds have been shown to be potent inhibitors of prolactin secretion both *in vitro* and *in vivo*. The drug is well tolerated, its major side effects being nausea and orthostasis - both of which can be minimized by initiating therapy with small doses and slowly advancing the dosage administered.

Numerous studies have demonstrated a marked suppression of serum prolactin levels in patients with prolactin secreting microadenomas. In a summary of 286+ women from 13 series (50), an average of 82% of patients had suppression of prolactin levels into the normal range. An equally high percentage of these patients had return of menses (94%) and improvement of galactorrhea (90%).

This high level of responsiveness demonstrated for microprolactinomas is also observed when such therapy is directed at patients with macroprolactinomas. In a summary of 119 patients with macroprolactinomas (50) 12/16 females (75%) and 6/11 males had normalization of prolactin levels. This normalization was accompanied by an improvement in visual fields in 23/26 (88%) and a demonstrable decrease in tumor size 18/52 (92%). More recent compilations of data (51) support these observations.

What results can be expected from such therapy? One paper that illustrates such a response is that by Thorner et al (52). In this work the authors demonstrated rapid changes in the size (by CT) of the tumor and visual fields in two patients with macroprolactinomas. These changes were paralleled by substantial improvements in the hyperprolactinemia. After one year of therapy, bromocriptine was discontinued with rapid regrowth of the tumor as evidenced by increased prolactin levels, increased adenoma size, and deteriorated visual fields. Similar results have been obtained by other investigators (53-56). This high response rate was observed in a prospective trial in macro- and microprolactinomas and led to the suggestion that "therapy with bromocriptine should be considered as initial management for patients with PRL-secreting macroadenomas" (57) - a conclusion that seems justified, in light of the available evidence. Most studies suggest that such therapy is rapidly effective in responsive tumors and within a few weeks, prolactin levels have fallen to their nadir levels. Maximal improvement is usually evident in 6 months as assayed by return of menses, fertility, and testosterone levels (in men).

Even in the very impressive data that I have already reviewed, a small number of patients - both in the micro- and macroprolactinoma categories - do not respond appreciably to bromocriptine therapy (50, 58). It is not clear what the basis of this resistance might be. Secondly, a small number of patients are not able to tolerate bromocriptine due to side effects. In some cases, such patients have been managed with other dopaminergic agents such as pergolide (59) or other newer compounds (60). Finally, it is obvious that some patients will present in situations where a timely assessment of tumor responsiveness may not be possible (e.g., rapid progressive impairment of visual fields). In such cases, neurosurgical decompression is the only viable alternative. Although some investigators have suggested that bromocriptine therapy can be stopped after several years (and some reports of 'permanent' cures have been reported), most people consider that such therapy should be continued for the life of the patient.

Is bromocriptine effective in the treatment of other tumors? This has been explored most extensively in patients with poorly controlled acromegaly. This effort followed initial reports that L-Dopa (61) in vivo and dopamine in vitro (62, 63) could suppress GH secretion. The results of bromocriptine in 514 acromegalic patients in 28 series is tabulated in Ref. 64. It is important to note that while a significant number of cases achieved GH levels <10 µg/L (54%), only 21% showed GH to less than 5 µg/L and only 7/88 (8%) patients showed the normalization of IGF-I levels. More importantly, only a limited number of studies (summarized in Ref. 64) examined objective indices of improvement. In such studies, it is evident that the objective and subjective responses observed with bromocriptine therapy are not in step with the levels of improvement observed in measurements of somatomedin-C or GH (66-68). Thus, while a trial of bromocriptine is certainly justified as an adjunctive measure in the control of acromegalic patients, it is clearly much less effective that when employed for the therapy for prolactinomas. The data for the use of bromocriptine in other tumor types is even less encouraging.

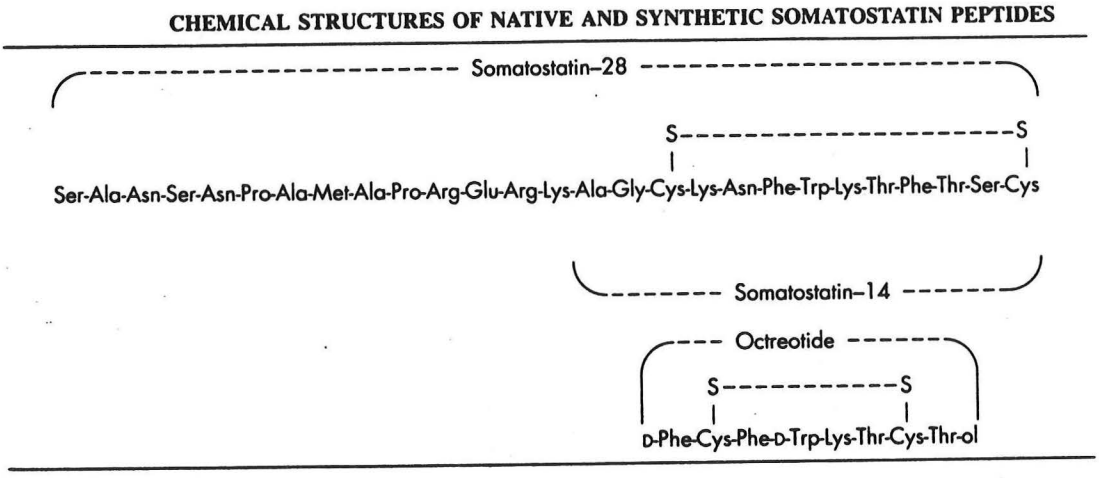


Figure 5

SOMATOSTATIN ANALOGUES

Efforts to medically control growth hormone secretion centered on the use of compounds related to somatostatin, as numerous studies had demonstrated a profound inhibition of GH by somatostatin secretion. Despite this in vitro efficacy, the short biological half-life of the native somatostatin molecule made it completely unsuitable for any meaningful therapeutic role. By manipulating the primary structure of somatostatin, chemists at Sandoz succeeded in synthesizing a compound that was both potent and much longer lived (69). Thus, in comparison to the nature somatostatin analogue, sandostatin (aka, SMS 201-995 aka octreotide) was more potent using in vitro and in vivo assays of GH inhibition. This compound also has a substantially longer half-life, in the range of 110 minutes (70). An unexpected feature of this molecule is that it is selective for GH, inhibiting GH secretion 45 more potently than native somatostatin, while inhibiting insulin and glucagon secretion only 11 or 1.3 times as well as native somatostatin, respectively.

TABLE VI

Growth hormone and SM-C responses (mean ± SE) to SMS 201-995 therapy (Tx)

Grade	Patient no.	SMS 201-995 dose (μg d)	Basal GH (mU/l)		Nadir GH after OGTT (mU/l)		Mean 12-h GH (mU/l)		Basal SM-C (IU/L)	
			Pre-Tx	Tx	Pre-Tx	Tx	Pre-Tx	Tx	Pre-Tx	Tx
Normalized	1	300	52	1·4	20·4	<0·4	42·4±6·0	1·0±0·2	7·9	1·0
	6	600	15·2	3	15·6	5·4	39·6±7·8	5·6±0·8	7·8	1·5
Effective	3	900	76	23	66	15	64·4±9·2	25·6±5·2	27·2	13·5
	5	900	62	7	46	4·4	146·6±16·8	7±0·4	8	2·5
	8	900	200	14·2	176	24	237·6±18·2	14·6±3·4	10	1·9
	9	600, 900	48	7·4	56	19·6	31·4±4·8	7·8±0·4	12·8	1·9
Improved	2	1500	25	11·2	14·4	5·4	17·2±1·4	11·8±2·0	15·5	2·4
	4	300	45·6	17·6	36	22	44·8±2·8	10·8±18	8	2·4
	7	900	16	10·8	13·4	11·2	18±0·8	7·6±0·8	8·1	2·6
Ineffective	10	900	68	100	76		115±13·4	173·2±31·2	11	10

A number of studies (for example, Refs. 71-77) have attempted to define the therapeutic effectiveness of sandostatin in the treatment of acromegaly. These studies demonstrate that sandostatin is effective in controlling GH secretion in acromegaly. In a compilation of several representative series (64), 55-80% of patients normalized measures of GH secretion and approximately demonstrated normalization of IGF-I levels. In concert with this hormonal effect, a dramatic clinical (subjective and objective) response could be demonstrated. Furthermore, in series in which reliable measurements have been obtained, sandostatin has a demonstrable effect on tumor size (77, 78). This effect, which is modest in magnitude, is most likely due to an effect on the size of the individual tumor cells, and not to a cytotoxic action of sandostatin.

Despite these positive qualities, sandostatin has several drawbacks. First, it has inhibitory effects on a variety of endocrine organs. This effect is most obvious upon insulin secretion by the pancreas, an effect which is most pronounced at higher daily doses (77). The side effect that appears to have the greatest potential to limit its widespread use in acromegaly is its effect on the contraction of the gall bladder. It is also an expensive medication to employ as chronic therapy ($15 per day at a dose of 100 μg tid). Current guidelines (79) suggest that it be employed as an adjunctive measure in patients that are not neurosurgical candidates, or who have not responded well to neurosurgery or radiation therapy.

APPROACH TO THE PATIENT

Initial Evaluation

Whatever the therapeutic options that are subsequently employed for a patient with a pituitary tumor, certain information is desirable prior to embarking on therapeutic maneuvers. First, the thyroid, adrenal, and gonadal

status of the individual should be established. This should be determined for two reasons: first, to determine whether preoperative hormone replacement is necessary, particularly with glucocorticoids or thyroid hormone. The second is to eliminate the possibility that end organ failure has led to pituitary hyperplasia. As noted above, cases of primary hypogonadism and hypothyroidism have been described in which such hyperplastic growth has masqueraded as a pituitary tumor (24-26, 80). It is essential as well that a serum prolactin level be determined preoperatively, as the identification of a tumor, even a macroadenoma, as prolactin-secreting radically alters the therapeutic options available. Additional samples should be obtained for measurements of FSH, LH, and α subunit, principally to serve as tumor markers. While extensive preoperative evaluations of endocrine function are carried out at some centers, these are carried out principally as part of ongoing research protocols and have no place in routine clinical practice.

Consequences of Therapy

The goal of any of these therapies is to remove or destroy the adenomatous tissue while preserving the residual function of the remaining normal pituitary tissue. It is often not possible to accomplish this in a completely selective manner. Thus, substantial normal pituitary tissue may be removed during a surgical procedure, damaged by radiation, or simply killed by the pressure effects of the tumor itself.

Interestingly, however, surgical decompression itself may restore a substantial pituitary function. Arafah et al (81) reported the results of detailed endocrine testing in 26 patients with large "non-secreting" pituitary adenomas. In this study, a substantial number of patients were found to have demonstrable deficiencies of GH (100%), gonadotropins (96%), thyroid (81%) and adrenal function (62%) preoperatively. These same patients underwent transsphenoidal tumor resection were then reevaluated 2-3 months later to assess the level of residual pituitary function. This author found that thyroid function, adrenal function, and gonadal function recovered in 57%, 38%, and 32%, respectively, in which deficiencies were identified preoperatively. By contrast, GH deficiency persisted in 85% of the patients. An interesting correlation was noted by these authors. That is, they found that the level of preoperative prolactin was correlated with a recovery of pituitary function. Thus, no patient with a preoperative serum prolactin <5 recovered any pituitary function, while those with the highest level of prolactin (>20) recovered the highest percentage of pituitary function. While the authors do not speculate on this observation, it would seem plausible that the elevated prolactin in this situation is a marker for the amount of remaining anterior pituitary that remains, but that has been removed from the inhibitory (on prolactin) or trophic (on the other anterior pituitary hormones) influences from the hypothalamus. Other studies have suggested that medical therapy of prolactinomas may be accompanied by substantial return of pituitary function (82).

TABLE VII

Recovery of pituitary, thyroidal, adrenal, or gonadal function in patients with large nonfunctioning pituitary adenomas presenting with hypopituitarism

Preoperative serum PRL level (ng/ml)	n	Pituitary function recovered			
		TSH	ACTH	Gonadotropins	GH
<5	5	0/5	0/5	0/5	0/5
5–20	9	5/8	1/5	3/9	0/9
>20	12	7/8	5/6	5/11	4/12
Total	26	12/21	6/16	8/25	4/26

The denominator represents the number of patients with documented deficiency of the particular function preoperatively. The numerator represents the number of patients who recovered that function.

There have been no suggestions in the literature that assessments of the recovery of pituitary function postoperatively or following medical treatment are inaccurate predictors of subsequent pituitary function. By contrast, there is ample evidence that vigilant retesting of endocrine function is required following radiation therapy of pituitary tumors (47, 48, 83, 84). In one series of patients, Snyder et al (83) examined the course of 35 male patients treated with surgery, radiation plus surgery, or radiation alone. In this series, he found that those patients treated with radiation and surgery exhibited the highest frequency of subsequent hormonal deficiency. Those patients treated with radiation alone had lower frequency of appearance, and surgery alone was rarely associated with subsequent pituitary insufficiency. While these authors noted several possible explanations (relating to preoperative extent of disease), the similar initial frequency of hormonal deficiencies led them to implicate the larger field size employed and to suggest that at least a portion of the deficiencies were due to the inclusion of the hypothalamus in the field ports (84). The incidence of insufficiency in another series (47) was substantial with 20% of patients manifesting secondary adrenal insufficiency and 13% manifesting secondary thyroid insufficiency. These results underscore the need for careful postoperative evaluations and followup in those patients following treatment, particularly those treated with the combination of radiation and surgery.

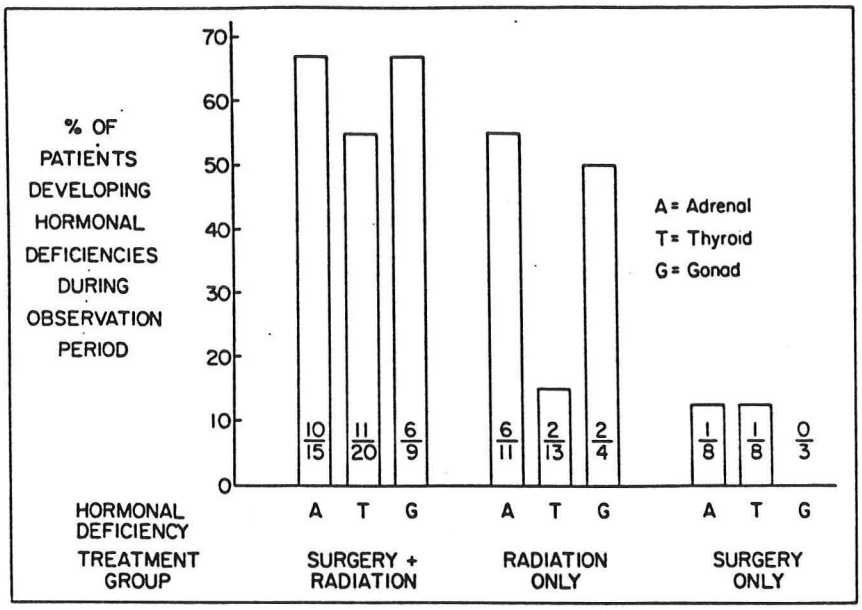


Figure 6. *Percent of patients in each of the three treatment groups (surgery plus radiotherapy, radiotherapy only, and surgery only) with deficiencies of adrenal, thyroid, and gonadal function during the four to five-year observation period. Within each bar, the denominator indicates the number of patients in each group whose adrenal, thyroid, or gonadal function was normal at the beginning of the observation period, and the numerator indicates the number in whom it became subnormal during the observation period. Contingency table analysis showed that the development of adrenal, thyroid, and gonadal deficiencies combined depended on the treatment group ($p < 0.005$). A greater proportion of the patients in the surgery plus radiotherapy group demonstrated deficiencies than did those in the radiotherapy only ($p < 0.05$) or surgery only groups ($p < 0.005$), and a greater proportion of the patients in the radiotherapy only group demonstrated deficiencies than did those in the surgery only group ($p < 0.05$).*

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