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Transsphenoidal Microsurgery for Selective Removal of Functional Pituitary Microadenomas

KARL D. NIELSON, M.D.*, CLARK WATTS, M.D., and KEMP CLARK, M.D.

Section of Neurosurgery, University of Missouri Medical Center, Columbia, Missouri, U.S.A and Division of Neurosurgery, Southwestern Medical School, Dallas, Texas, U.S.A.

The transsphenoidal approach to the pituitary gland is emerging as the safest and most efficacious procedure for the management of pituitary tumors. With the aid of the microscope large tumors producing visual symptoms can be removed and microadenomata producing only signs and symptoms of endocrinopathies can be safely and adequately approached. The procedure is described in this report. The results of its use in 29 patients with selected illustrative case reports are described.

Transsphenoidal microsurgery is returning as the safest and most effective procedure in the management of pituitary tumors. Developed in 1905 [1] and improved over the next few years [2], this technique was used by Cushing for many of the patients in his large series [3]. He abandoned it because of poor visualization, postoperative cerebrospinal fluid (CSF) rhinorrhea, and meningitis. The use of the operative microscope, televised fluoroscopy, and microneurosurgical instruments and techniques has revivified the operation. Guiot [4], initially, and Hardy and co-workers [5, 6] have made important contributions to the development of the present transsphenoidal operation especially for microadenomata of the pituitary gland. The authors have used this approach almost exclusively during the last 3 years. Transcranial surgery has been reserved for very large or eccentrically placed tumors. A total of 29 cases of pituitary tumors have been operated on, including 10 cases of nonhormonally active chromophobe adenomas and 19 functional adenomas. Functional tumors include 15 growth hormone–secreting tumors, 3 prolactin-secreting neoplasms, and 1 adrenocorticotropin-secreting tumor. These cases form the basis for this article. In addition to our experience with tumors, 3 patients with cerebrospinal fluid rhinorrhea [7] have undergone successful transsphenoidal surgery. Three patients have undergone transsphenoidal hypophysectomy for palliation in metastatic carcinoma.

Selected Case Reports

Case 1

Nelson's Syndrome (ACTH-Secreting Pituitary Microadenoma). At age 24, this patient developed amenorrhea, noncentrifugal obesity, easy fatigability, polyuria and polydipsia, moon facies, abdominal striae, webbed neck, hypertension, and hypothyroidism. She was evaluated endocrinologically and found to have elevated urinary 17-hydroxycorticosteroids [10.7 μg%; normal (N) = 2 to 6 μg%] and elevated urinary 17-ketosteroids (23.4 to 78.9 μg%; N = 6 to 26). A dexamethasone suppression test suggested an adrenal origin of her Cushing's syndrome. Adrenal arteriograms revealed no abnormalities. One month later bilateral adrenalectomies were performed. Only adrenal hyperplasia without adenomata was found. Within 2 months she developed increased skin pigmentation and postural hypotension. Despite increased doses of exogenous steroids (hydrocortisone and fluorocortisone acetate), her skin continued to darken. One year later she was found to have a plasma cortisol level of 2 μg%. Neuroophthalmologic examination revealed an inferior incongruous quad-

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Reprint requests: Doctor Clark Watts, Section of Neurosurgery, University of Missouri Medical Center, Columbia, Missouri, U.S.A. 65201.

rantanopsia for red objects. ACTH levels in her serum were at values ranging from >1500 to 4750 pg (N = 890). She was discovered to have bilateral galactorrhea with a prolactin blood level of 43.5 ng/ml (N = 10 to 20 ng/ml). Sella turcica polytomography revealed no asymmetry, erosion, or thinning. Pneumoencephalography revealed an "empty sella." Transsphenoidal selective microsurgical removal of a pituitary microadenoma was performed. Postoperatively the patient did well except for persistent polydypsia and polyuria requiring use of fluorocortisone acetate. Postoperative data showed a reduced prolactin level of 24 to 28 ng/ml. (Prolactin levels may reflect the chronic use of phenothiazines and amitriptylene hydrochloride.) Postoperative ACTH levels do not reflect the normal ACTH compound found preoperatively, and the patient and her ACTH-like compound are currently under intensive investigation.

Case 2

Prolactin-Secreting Pituitary Microadenoma. A 26-year-old nulligravida presented with anovulatory amenorrhea. She had had one episode of menstrual bleeding induced by an estrogen-progestin compound. Physical examination was normal except for bilateral profuse galactorrhea and loss of endocervical mucous. The only blood hormone abnormality was prolactin levels in the 190 to 218 ng/ml range, normal being 10 to 20 ng/ml. Sellar polytomography revealed the sella to be at the upper limits of normal in size with an anterior bulge on the right side of the floor. The right anterior portion of the sellar floor was clearly thinner than normal. Visual fields by Goldman perimetry were normal.

Transsphenoidal selective removal of an acidophilic pituitary microadenoma from the right anterior inferior portion of the sella was performed. The patient was noted to have dryer, smaller breasts at discharge from the hospital on the fifth postoperative day. By postoperative day 23, only one drop of milk could be expressed from each nipple. Prolactin levels at that time had fallen to 72 ng/ml.

Case 3

Prolactin-Aldosterone–Secreting Pituitary Microadenoma. The patient was a 54-year-old woman who had been treated for hypertension since 1964. She was found to have primary hyperaldosteronism in 1974 and underwent a venogram which revealed a probable left adrenal mass. Left adrenalectomy revealed micronodular hyperplasia but no tumor. Hypertension and hyperaldosteronism persisted. Multiple prolactin blood levels were 75 to 255 ng/ml. (Most were above 120 ng/ml.) Aldosterone levels were 25 to 50 ng/100 ml. (N < 20 ng/100 ml.) In April 1975, sella polytomography revealed an asymmetrical sellar floor with the right side lower and thinner than the left. In July 1975, the patient had a normal cerebral arteriogram. Transsphenoidal pituitary surgery revealed an acidophilic microadenoma on the right side of the sella. Postoperative prolactin and aldosterone activity are being actively investigated in an ongoing study.

Case 4

Acromegaly Associated with Chromophobe Pituitary Adenoma. This case is selected as an example from among our 15 acromegalics treated with transsphenoidal surgery. The patient is a 41-year-old man who was noted by an endocrinologist friend to be developing acromegalic features. He was admitted to the hospital with malignant hypertension. Appropriate therapy brought his blood pressure under control. An evaluation for acromegaly was done and confirmed the endocrinologist's observations. Growth hormone levels were 25.5 and 42.8 ng/ml, normal range being <5 ng/ml. An enlarged sella turcica with erosion of the right side of the floor was found.

Sellar laminography confirmed the plain X-ray findings. Pneumoencephalography revealed no extra or suprasellar extension of tumor. Transsphenoidal removal of a chromophobe adenoma was successfully performed. He was discharged on the fifth postoperative day. His acromegalic features softened and growth hormone levels fell to 0.7 ng/ml after surgery. His other pituitary functions continue in the normal range.

Technique of Surgery

The patient is placed in a semisitting position with the head turned slightly toward the operator. A mobile C-arm radiofluoroscopic image intensifier is placed to allow a lateral view of the sella turcica on the television monitoring screen. The image intensifier is activated briefly as the vomer bone is approached, but more frequently as the transsphenoidal and intrapituitary phases of the operation are performed. This provides rapid and safe access to the desired site with close monitoring avoiding improper placement of instruments laterally near the cavernous sinus or too deeply through the diaphragma sella into the optic chiasm or brainstem. The operating microscope is placed within the circle of the image intensifier arms for visualization of the opened sphenoid sinus and the sellar contents.

General endotracheal anesthesia is used in all cases. The oralpharyngeal cavity is packed with mois-

tened 2-inch gauze. The patient's face below the eyes, his nasal cavities, and upper gingiva are cleansed with Betadine® (RTM) solution. The medial and inferior nasal mucosa and the upper anterior oral gingiva and mucosa are infiltrated with sterile normal saline solution containing aqueous epinephrine in a concentration of 1:250,000. A small area on the anterolateral right thigh is draped separately after routine surgical preparation to obtain fascia lata and muscle for packing the opened pituitary fossa at closure.

A horizontal incision is made through the mucosa of the upper lip from one canine fossa to the other. The upper maxillary ridge and frontal nasal spinous process are exposed by submucosal elevation with staphylorrhaphy dissectors (Fig. 1A). The maxillary ridge and the frontal nasal spinous process are removed with a small, sharp osteotome. A submucous resection of the inferior one-third of the cartilaginous nasal septum is performed. The mucosa should be elevated intact as perforation may allow potential contamination. A bivalve nasal speculum, directed toward the floor of the sphenoid sinus under fluoroscopic control, is inserted into the submucosal cavity thus created. The septum is removed sharply with a swivel knife or piecemeal with small Jansen-Middleton rongeurs. A larger Cushing transsphenoidal self-retaining retractor is substituted for the nasal speculum after the vomer is exposed (Fig. 1B). The keel-shaped vomer is detached by grasping it with a pituitary rongeur. This bone is saved, as are the portions of the septum, to insert in the open floor of the pituitary fossa during closure.

The operating microscope is brought into use at this time and the remainder of the operation is performed using magnified three-dimensional vision. The excellent illumination provided is most beneficial. Further removal of the floor of the sphenoid is done with the Kerrison punch. The suction cautery is employed to exenterate all visible sphenoid sinus mucosa.

Access to the anterior and inferior sections of the floor of the sella is gained. A midline window is made

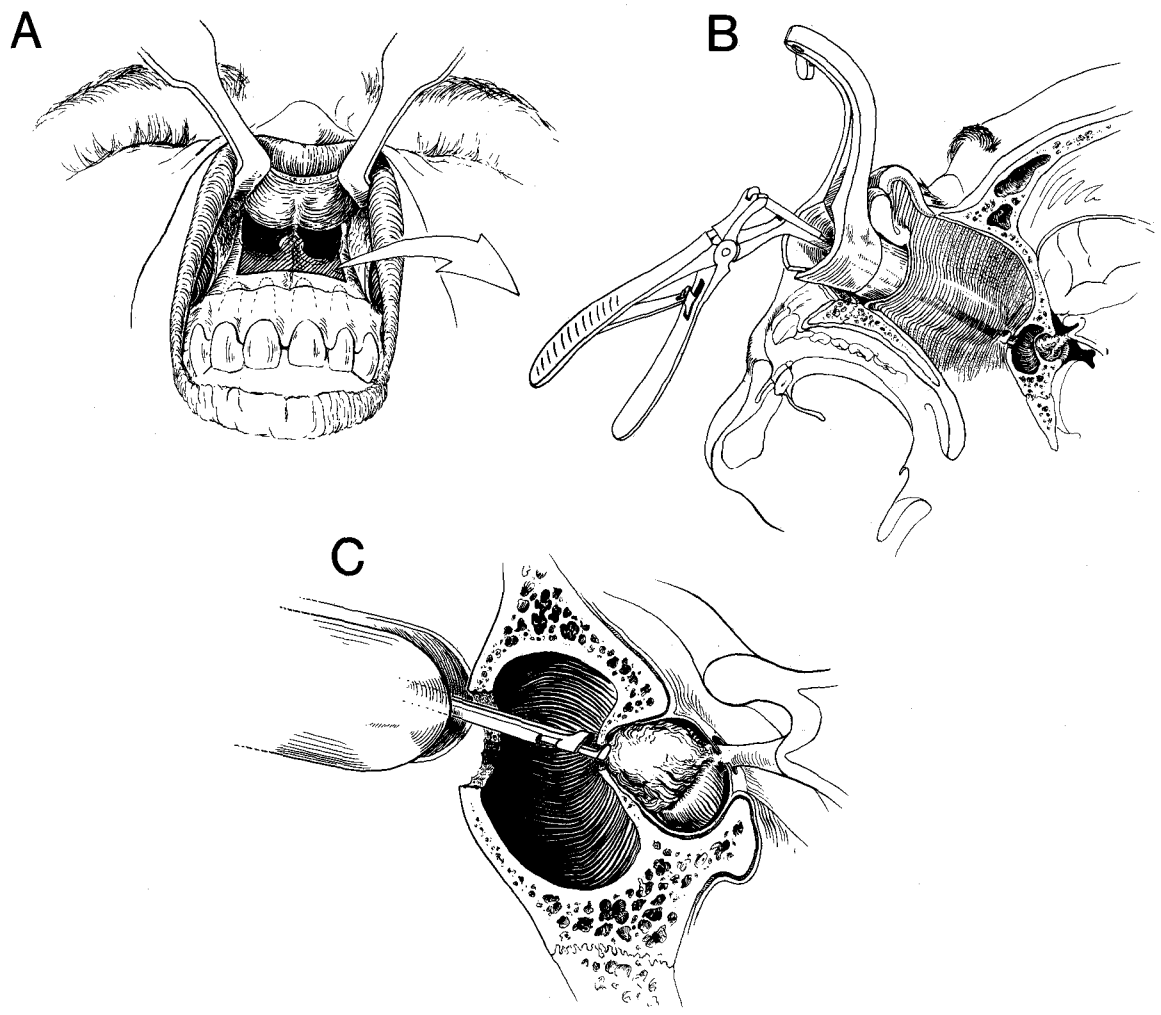

Fig. 1. Transsphenoidal approach to the sella turcica (see text for detailed explanation of figure)

in the sella floor with a small osteotome. Bone is then resected until an adequate opening for intrasellar manipulation is provided (Fig. 1C). This is usually about a 1.0- to 1.5-cm opening. The dura in the sella is reflected to permit controlled opening of the gland. A transverse or T-shaped dural incision is made and the dura separated from the pituitary gland. A small adenoma or totally replaced adenomatous pituitary gland may extrude itself separating easily from the firm, normal anterior pituitary parenchyma. Sometimes it is necessary to separate a firm microadenoma from the gland with blunt instruments (Fig. 2D, E). Specimens of hormonally active pituitary tumors are saved for routine pathologic studies, electron microscopy, and cell culture.

Closure is simple. Muscle and fascia lata, obtained from the thigh, are placed in the pituitary fossa (Fig. 2F) and secured by a piece of cartilaginous septum or vomer slightly larger than the opening in the sella. This bone is inserted under the rim of opened sellar floor (Fig. 2G). This maneuver helps prevent CSF leak by keeping the muscle from falling into the submucous space. The nose is packed with a gauze strip soaked in antibiotic ointment. Closure of the labial mucosal incision is optional.

Results

In the group of 15 acromegalics, all but 4 patients achieved normal growth hormone levels postoperatively. Two were below 10ng/ml and the other two achieved levels near normal after reoperation. The other patients with prolactin-secreting tumors have shown decreasing levels of prolactin and decreased galactorrhea but have not achieved normal prolactin levels. Two patients in the entire series developed nausea, vomiting, and low serum sodium and potassium levels transiently 1 week postoperatively. This was easily corrected by fluid and electrolyte therapy. There were no other complications.

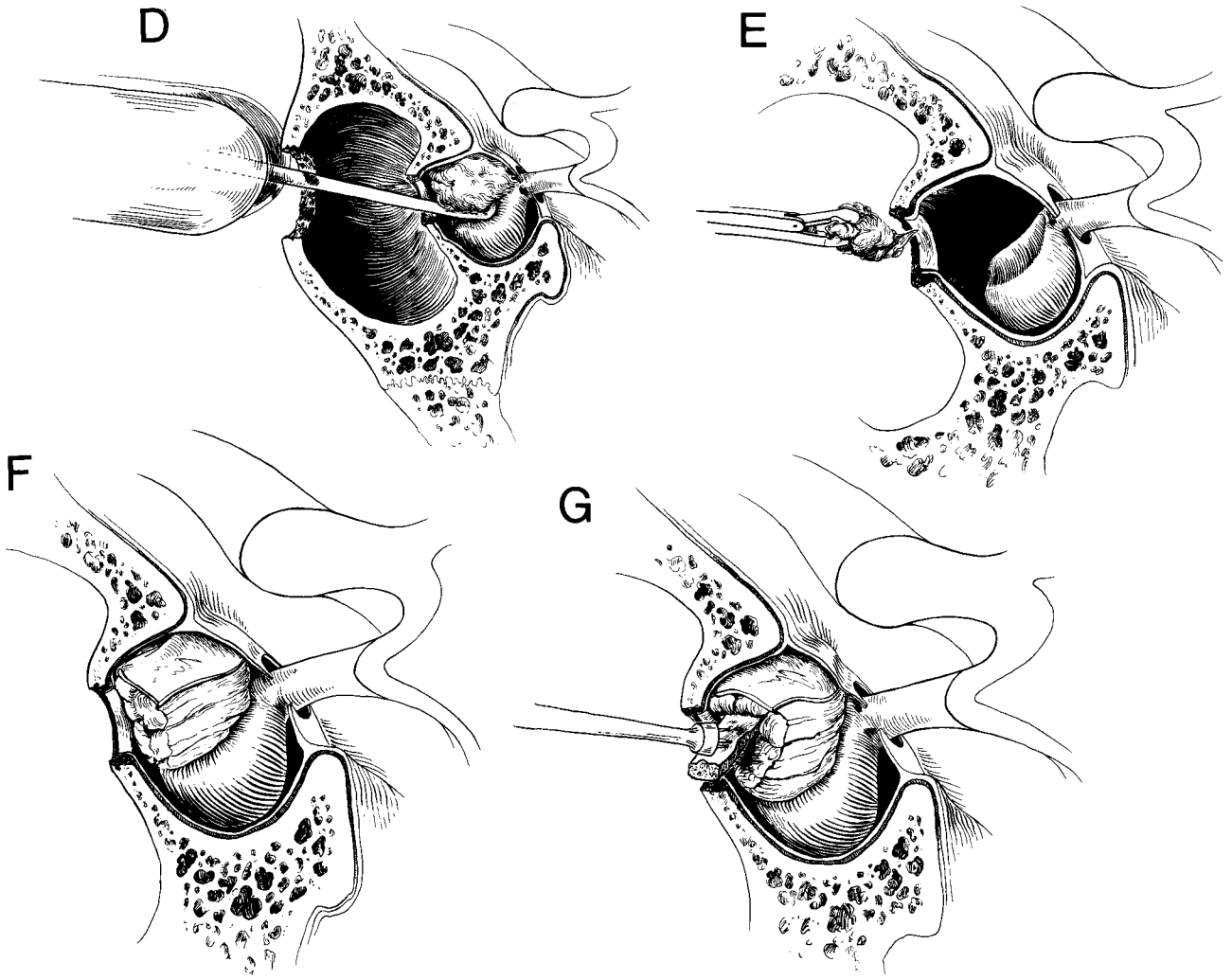

Fig. 2. Removal of adenoma of the anterior pituitary via transsphenoidal route (see text for detailed explanation of figure)

Discussion

Clinical cases of excessive secretion of anterior pituitary-mediated hormones have been reported involving prolactin (galactorrhea, amenorrhea, and infertility), ACTH (Cushing's diseases and Nelson's syndrome), somatotropic hormone (gigantism and acromegaly), thyrotropin (hyperthyroidism), and, rarely, excessive follicle-stimulating hormone (FSH) associated with eunuchoidism. Well-established and reproducible assays are available for each pituitary hormone [8], and in combination with provocative and suppressive tests, it is now possible to identify with some accuracy and confidence those patients with secreting tumors. Polytomography, selective angiography with subtraction and magnification, and pneumoencephalography (especially with polytomography) are most helpful procedures in determining if a pituitary tumor is the source of the excessive hormone.

The establishment of the diagnosis of a hypersecreting tumor is usually an indication for its surgical removal. No other therapy is capable of returning the patient toward a normal endocrinologic status in a large number of cases. Transsphenoidal surgery for such tumors allows successful removal of the functional adenoma and preservation of normal pituitary function in a gratifying number of patients. This series of transsphenoidal operations, like others, is free of significant morbidity with no mortality to date [4, 6, 9–13].

Prolactin-secreting adenomas are the most frequently diagnosed functional pituitary tumors and represent perhaps 25% of all pituitary tumors [14, 15]. In the past they have not been treated surgically as craniotomy and complete hypophysectomy entail excessive risk. First described in 1954 and sometimes called the Forbes-Albright syndrome [16], the syndrome of nonpuerperal galactorrhea, amenorrhea, low urinary FSH, and infertility may be safely corrected by the transsphenoidal operation without interfering with normal anterior and posterior pituitary function. Our series of 3 cases demonstrates this favorable outcome. Baseline levels of serum prolactin greater than 25 ng/ml (N = 10 to 20 ng/ml) and failure of phenothiazine drugs to induce a significant rise in prolactin levels, as occurs in normals, combined with the clinical signs and symptoms establish the diagnosis. These tumors (usually acidophilic adenomas) are present in both men and women. Surgery may be indicated in patients strongly desirous of fertility and to avoid the annoyance of galactorrhea and amenorrhea. Radiation therapy and drugs have been ineffective [15]. The ultimate role of surgery is not yet fully determined.

Somatotropic (growth) hormone results in gigantism in prepubertal patients and in acromegaly thereafter. Correct and early diagnosis is possible due to availability of the HGH assay. Significant morbidity and shortening of life complicate the course of patients with these tumors making effective treatment clearly indicated. Diabetes and bone, muscle, and cardiovascular diseases are late manifestations. Transsphenoidal surgery is the preferred treatment. Standard irradiation therapy does not reduce growth hormone levels to normal and bring the disease under control. Heavy particle irradiation appears to be effective but is available in only a few centers [17]. The long-term effects of such radiation on surrounding tissues is unsure. Other surgical methods, such as cryosurgery, are less sure, or, like craniotomy, less safe than transsphenoidal microsurgery.

Cushing's syndrome may be caused by multiple sources of increased adrenal corticosteroids. Cushing's disease, which is hypersection of pituitary adrenocorticotropic hormone, is most likely due to a functional microadenoma of the anterior hypophysis. Cushing's syndrome, on the other hand, may be due to adrenal adenomas. Cushing's disease can be differentiated from Cushing's syndrome by determination of elevated serum ACTH and by the dexamethasone suppression test. Corticosteroid secretion is suppressed when high doses of dexamethasone are given for several days if an adrenal adenoma is present. Transsphenoidal excision of the pituitary microadenoma is the treatment of choice. Nelson's syndrome [18], consisting of elevated ACTH levels and related skin hyperpigmentation, occurs in a small percentage of patients after bilateral total adrenalectomy for Cushing's syndrome. A pituitary microadenoma, probably present before adrenalectomy, is the cause. Again, the transsphenoidal approach is the treatment of choice.

Familiarity with the oronasal-transsphenoidal approach, skill and practice with the use of the operating microscope and microinstruments, access to laboratory facilities capable of performing the requisite assays, and availability of appropriate, sophisticated equipment for the operation are important prerequisites for the performance of successful transsphenoidal surgery. With these requirements met and with experienced surgeons operating on properly selected patients, the transsphenoidal approach to pituitary surgery is useful, safe, and preferred, in most cases.

Résumé

L'approche trans-sphénoidale dans la chirurgie de l'hypophyse est en voie de devenir la technique de choix dans le traitement des tumeurs hypophysaires. L'emploi du microscope permet d'exciser non seulement les tumeurs volumineuses responsables de sym-

ptômes visuels mais aussi les microadénomes manifestés uniquement par des syndrômes endocrinologiques et ceci adéquatement et sans risque. L'article décrit la technique et rapporte les résultats obtenus chez 29 patients en plus de présenter en détails quelques cas choisis pour leur représentativité.

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INVITED COMMENTARY

JULES HARDY, M.D., F.R.C.S.(C) F.A.C.S.

Notre-Dame Hospital, University of Montreal
Montreal, Canada

Doctors Nielson, Watts, and Clark have reported their early experience in a series of 29 cases of pituitary adenomas operated on by the transsphenoidal approach during a period of 3 years. They should be congratulated for having encountered no mortality or morbidity, since difficulties often occur in the early experience with a new operation. However, the therapeutic results in their series are not as good as those that we have obtained since ¼ of the acromegalic patients had elevated growth hormone levels after surgery and none of the 3 patients with prolactin-secreting adenomas had normal prolactin levels postoperatively.

In our series of transsphenoidal removal of over 225 hypersecreting pituitary adenomas, which includes 100 cases of acromegaly, 100 cases of prolactin-secreting tumors and 25 cases of Cushing's disease, more than 50% of the patients had a normal sized sella turcica. Microsurgical exploration of the pituitary gland allowed detection and selective removal of an intrapituitary lesion smaller than 10 mm in diameter, which we have called a "microadenoma". In this group of microadenomas, clinical and biological cure was obtained after one operation in more than 80% of the cases. The main advantage of this method is that it allows identification and preservation of the normal pituitary gland so that the patient does not require hormonal replacement therapy. For tumors of larger size and for invasive lesions, selective adenomectomy is still possible but there is a higher risk of persistance of abnormal tissue or recurrence; thus, occasionally a second operation is required to accomplish a total sellar clean-out and definitive cure of the hypersecreting lesion.