Advances in the Management of Pituitary Tumors*

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A new development in the management of pituitary tumors is the transsphenoidal technique. It will be my purpose to show that it provides an elegant way of handling the great majority of pituitary problems, at least the ones that I have encountered, although it has its shortcomings as well as its advantages.

Pituitary tumors manifest themselves in two ways—by compressing structures in the neighborhood, primarily the optic nerves and chiasm and by the two endocrine manifestations, one being the compression of the normal pituitary gland to produce varying degrees of hypopituitarism and the other, the hyperfunctioning adenoma. A large tumor with a suprasellar extension compresses the optic chiasm and optic nerves; obviously, a tumor of this size would also cause a degree of hypopituitarism. A smaller tumor, a microadenoma, can express itself by hypersecretion of a hormone before it has either produced neighborhood signs or has compressed the normal gland to produce hypopituitarism. A functioning microadenoma secretes an excess of a particular hormone; we have encountered three neoplastic cell types that I will describe later.

We owe the transsphenoidal approach to Harvey Cushing, who took up the procedure because at that time it was safer than craniotomy. Dr. Cushing, working with a headlight (looking very much like a coal miner's lamp) and with a simple speculum, achieved excellent results. He encountered two problems—he was viewing a deep, dark hole without

magnification, and there was a CSF lead and meningitis without the advantage of antibiotics. A Frenchman, Guiot, is largely responsible for reintroducing the transsphenoidal procedure. One of his brilliant students, Jules Hardy, refined the technique, using the operating microscope and an image intensifier, which allows the operator, *during* the procedure, to observe operative maneuvers in the region of the sella.

The anatomical principles underlying the surgical approach to the pituitary are really two: One is a sublabial-transnasal-transsphenoidal approach, maintaining the strict midline which is of great advantage to the surgeon, because he can see equally well to the right and to the left and he knows that he is in the midline. The second is the image intensifier in the lateral projection, because this permits the surgeon to look on the television monitor so that he can approach the sella between the tuberculum and the floor; he can see his instruments within the sella, and he can put air in the ventricular system at the beginning of the operation and watch the third ventricle pulsate down into its normal position as the suprasellar component of the tumor is removed. For maximum safety, the image intensifier is essential. With experience, one can see and identify the normal pituitary gland, and the surgeon can be certain that the suprasellar component has been removed, because the normal intracranial pressure in a semisitting position forces the stretched diaphragm of the sella (which we have erroneously referred to as the tumor capsule in the past) back down into the sella, so that with a sizable suprasellar extension, one actually ends up with a diaphragm almost pulsating on the floor of the sella.

Dr. Hardy has recently suggested that microadenomas of certain cell types occur in preferential sites within the anterior lobe. This has not been our experience, but his larger experience is more valid. The endocrinologists with their elegant techniques can pick up endocrinopathies at an early stage. Our neuroradiology had to improve to identify a microadenoma, when the endocrinopathy was defined. This is particularly true, not so much in acromegaly, but with the galactorrhea-amenorrhea syndrome and postadrenalectomy Nelson's syndrome.

We are completing a paper on our experience with the neuroradiology of microadenomas. Although in the lateral projection, the sella is unremarkable, on plain films, lateral polytome cuts show an obviously abnormal sella. With A-P polytome cuts, one can predict the location of the microadenoma because of depression and thinning of the floor of the sella. The surgeon can expose the microadenoma at the site of the focal sellar bulging.

A microadenoma is 1 cm or less in diameter. These small tumors are ideally suited to transsphenoidal removal. One would not approach a microadenoma with the classical transfrontal technique, since it is difficult to reach and involves going through normal anterior pituitary at an awkward angle to reach the adenoma.

I have removed 60 pituitary tumors by a transsphenoidal approach; one-half presented with hyperfunctioning adenomas. My experience with these tumors has pushed me strongly in two directions: First, we have an extremely active endocrine group and a large number of acromegalic patients; second, I work with a neuro-ophthalmologist, William F. Hoyt, who attracts patients with unusual eye problems, a fair number of whom have pituitary disorders. Approximately one-fourth of his patients had clinical and chemical hypopituitarism at the time of presentation—11% complained of visual loss; 7%, of diplopia; 6%, of headache; and 4% had rhinorrhea. Regarding visual-field defects—58% had no defect, 32% had bitemporal hemianopsia or some variation of that, and 10% had some other type of visual-field defect.

By routine stains, 62% were chromophobe, 36% eosinophil, and 2% basophil. In the chromophobe group are some prolactin-secreting adenomas, some growth hormone-secreting adenomas, and some ACTH-secreting adenomas. According to functional types, 40% secreted nothing or, at least, nothing that we recognized. I suspect, however, that this number would be smaller, if we checked every patient for prolactin levels, because elevated prolactin levels can exist without any overt clinical manifestation. The remaining 60% secreted an excess of one hormone: 14% prolactin, 10% ACTH, and the remainder, growth hormone. All patients with ACTH-secreting tumors had undergone prior adrenalectomy and presented with hyper-pigmentation and high ACTH levels.

With respect to anatomical extent of the tumors, 33% were entirely intrasellar. Some of these were microadenomas; some were not. Even with very large sellas, the tumor may be contained within the sella. The remainder extended beyond the sella—some with extrasellar extension in more than one direction—42% were suprasellar, 28% had eccentric lateral extension, and 23% went into the sphenoidal sinus. The number of sphenoidal and suprasellar extensions is directly related to the quality of the neuroradiology.

When we began using the transsphenoidal technique, we got only the castoffs—patients who had failed to respond to prior treatment. Ours was the second team in terms of handling pituitary problems, but as we demonstrated our ability to handle recurrent tumors, we began seeing primary cases.

As we gain greater experience with the acromegalic patients, we are reducing growth hormone levels down to very low levels, like 2–3 ng/ml. Not a single patient, primarily treated for acromegaly, has developed hypopituitarism following operation. Transsphenoidal removal constitutes excellent treatment for acromegaly, and we are seeing more and more patients. We are in the process now of designing a study which will compare transsphenoidal removal alone with transsphenoidal removal plus irradiation. Unless postoperative growth hormone levels are in the normal range, the adenoma has not been removed. Because our experience is limited, we do not know how many of these patients will return with late recurrence.

Patients with Nelson's syndrome have undergone adrenalectomy for Cushing's disease, and at variable times thereafter, become hyperpigmented. Many tumors that secrete ACTH are malignant in the biologic behavior, which is a compelling reason to make the diagnosis and to treat them radically as soon as possible.

One of the more interesting facets of the microadenoma story is the syndrome of galac-

torrhea and amenorrhea. Historically, three types of galactorrhea and amenorrhea have been described, depending upon whether the syndrome appeared following delivery or spontaneously. The group of interest here is the Forbes-Albright syndrome, which can have its onset either postpartally or, more often, spontaneously. By definition, the sella turcica is enlarged, and galactorrhea and amenorrhea are permanent. The only difference between the Forbes-Albright and the Del Castillo syndrome is the normal sella, and here I think it is a matter of time. These patients have microadenomas, but until one studies the sella by polytomography, the sella may appear normal. We now have eight of these patients—three harbored macroadenomas and the remainder, microadenomas. These, like the ACTH-secreting adenomas, have a greater liability than the usual chromophobe adenoma to become invasive. For some reason, unlike the growth hormone-secreting adenomas or acromegaly, tumors that secrete prolactin and tumors that secrete ACTH are inherently bad actors; that is, they have a relatively high risk of becoming malignant as judged by invasive behavior.

Excluding one patient with an intrasellar abscess, we have had no operative deaths, and this is a significant advantage of the technique. We divided the morbidity into major and minor, the major including pneumonitis and rhinorrhea. If we think that the patient might be developing rhinorrhea, we treat vigorously in the first five postoperative days; I am certain that we are overtreating and unnecessarily treating a number of patients. We insert a lumbar subarachnoid drain, start Diamox®, and elevate the head; and our rhinorrhea rate falls very rapidly. Two patients had transient cranial nerve palsies due to vigorous use of a curette against the wall of an already compressed cavernous sinus. One patient had a postoperative hematoma within the tumor capsule. This was recognized within four hours, and the patient was returned to the operating room, where it was removed with no consequences. Five patients had diabetes insipidus persisting longer than a month and four patients had transient diabetes insipidus. An aseptic meningeal reaction from blood in the CSF, sinusitis, nose bleed, one corneal abrasion, and urinary tract infections represented minor complications. In no patient who had either normal or impaired vision prior to operation was vision made worse; this makes it a very attractive procedure, because even with the very best results from the transfrontal technique, vision was made worse in an occasional patient.

The transsphenoidal technique is the procedure of choice under the following circumstances.

1. Sphenoidal extension;
2. Modest suprasellar extension without lateral extension: We can handle the direct upward suprasellar extension. In the last 18 months, I have operated on 40 pituitary tumors, only one of which was done by craniotomy. There was a suprasellar extension that went laterally into one frontal lobe, and you simply cannot turn the corner going through the sphenoid sinus. Consequently, this patient was done transfrontally.
3. The patient with paracentral, bitemporal scotomas: The neuro-ophthalmologist will assure you that this patient has either a pre-fixed chiasm or a retrochiasmal nodule. This presents a difficult problem for the neurosurgeon operating transfrontally, because the optic nerves are hugging the tuberculum and there is no room to work between the optic nerves. This is, in my opinion, an indication, unless there is some contraindication, to the transphenoidal route.
4. The microadenoma (mentioned earlier);
5. Spontaneous rhinorrhea in association with a pituitary tumor;
6. Pituitary apoplexy: A low morbidity procedure accomplishes what you want to accomplish very quickly, and since these patients are often ill and need rapid decompression, I think it is clearly the procedure of choice for pituitary apoplexy.
7. The patient who is old or debilitated for whatever reason, or if you simply want to do a biopsy.

Which tumors should be approached by the transfrontal technique? Again, this is my own prejudice. The massive suprasellar extension is a huge mass of intracranial tumor, and what is happening within and immediately above the sella is really not the important part of the tumor. I have discussed the tumor with lateral extension. Perhaps tumors with massive suprasellar and sphenoidal extensions should be removed sequentially by both routes. The one contraindication to any major procedure is unequivocal cavernous sinus invasion. Extraocular motor palsies

alone are not an indication of invasion. As pointed out by Sir Geoffrey Jefferson, a fixed sensory loss is the one clinical sign of cavernous sinus invasion.

In summary, the one thing that is new in the management of pituitary tumors is the transsphenoidal technique. Obviously, there still remains a place for transfrontal craniotomy and cryosurgery, but I predict that an increasing number of pituitary tumors will be done by the transsphenoidal technique.