Surgical Management of Cushing's Disease: A Personal Perspective

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What about Cushing's disease differs from the other types of pituitary tumors? There are several differences, of course, but one of the principal differences is evident from inspection of Figure 1, in which this young boy's spin-echo magnetic resonance image (MRI), performed on an MR scanner with a 3-T magnet, does not demonstrate his tumor, despite the fact that he has severe clinical manifestations of Cushing's syndrome. The small tumors that cause Cushing's disease present unique challenges for diagnosis and treatment; that has been so from the very beginning.

HISTORY OF SURGERY FOR CUSHING'S DISEASE

Harvey Cushing described his first patient with what we now know as Cushing's disease, Minnie G., 100 years ago in December of 1910, and although he recognized that she had a distinct clinical syndrome, he had no way of determining what was causing it.[1] The function of the pituitary gland was poorly understood at the time—cortisol was not to be isolated and identified for another 40 years—but he did recognize that the syndrome might be related to the pituitary and included her in his 1912 monograph *The Pituitary Body and Its Disorders*.[1] Twenty years later in ''The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism),'' he described 12 patients, including Minnie G., who had the typical features of Cushing's syndrome, the general clinical syndrome caused by long-term exposure to excess glucocorticoid levels.[2] Most of the patients that he presented in his monograph had died of complications associated with the syndrome, and autopsy had demonstrated small basophilic pituitary tumors. However, very little surgery was done for patients with a diagnosis of Cushing's disease for the next 7 decades.

It was not until the early 1980s that pituitary surgery became the initial treatment of choice for patients with Cushing's disease. Although surgery was rare before then, it was performed occasionally. Two of Cushing's students, Drs Pattison and Naffziger, surgically explored the pituitary in 1933, the year after Cushing's monograph was published. Dr Naffziger's strategy, and one that he attempted, was to remove the offending tumor; this was the first attempt to remove a tumor in a patient with Cushing's disease.[3,4]

What happened between 1930 and 1980 to persuade the medical and surgical communities that the problem was not in the pituitary? Shortly after Cushing's monograph was published, the focus of determining the presumed basis of the disease became the adrenal; this focus was stimulated by 2 reports, 1 published in 1935 by Susman[5] and 1 in 1936 by Costello.[6] These authors examined the pituitary glands of patients who died of other causes and found that a surprisingly large fraction of patients, 9% in Susman's article and 22% in Costello's study, had incidental pituitary adenomas at autopsy, many of which were basophilic adenomas. Thus, shortly after Cushing's contribution had been widely acclaimed for its scholarship and importance, the basophilic adenomas that he had described were considered incidental findings rather than the cause of Cushing's syndrome, and the focus shifted to the adrenal for the next 40 years.

It was Jules Harding, shortly after he introduced the operating microscope for pituitary surgery in 1962, who recognized that tumors can also be small and that selective adenomectomy is an effective surgical strategy. The following year, he performed the first selective adenomectomy for Cushing's disease, and that patient is still doing well 48 years later.[4] It was the series of patients presented by Hardy at a conference on the diagnosis and treatment of pituitary tumors at the National Institutes of Health in 1973[7] and subsequent publications of series of patients by Hardy,[8] Salassa et al,[9] and Tyrrell et al[10] that persuaded the medical and surgical communities that the source of the disorder was the pituitary gland, and only after that did neurosurgeons become regular participants in the treatment of patients with Cushing's disease.

SURGICAL TREATMENT OF CUSHING'S DISEASE

For Cushing's disease, as in all other types of pituitary tumors, we endeavor to eliminate the tumor immediately and completely while preserving pituitary function and avoiding complications. These goals can be achieved in most but not all patients. In 2 large multi-institutional studies, 70% to to 80% of

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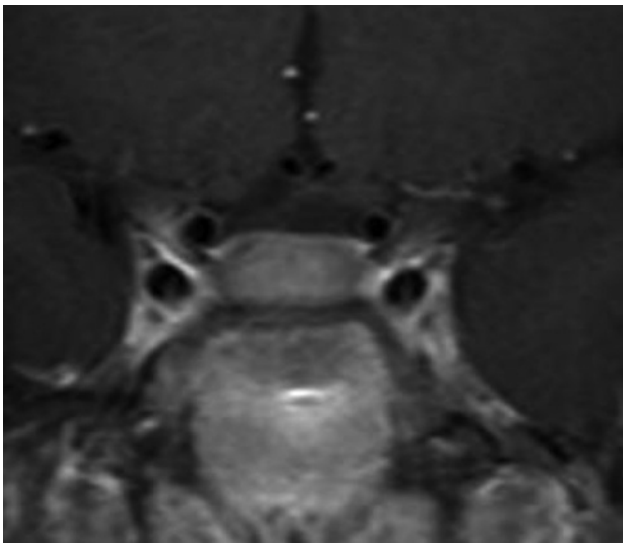

FIGURE 1. No adenoma is visible on this coronal postcontrast spin-echo pituitary MRI of a young boy with Cushing's disease, despite the fact that this MRI was performed on a 3-T MRI scanner.

patients who underwent surgery for Cushing's disease had remission after selective adenomectomy (defined as resolution of hypercortisolism, including hypocortisolism and eucorticolism), and 20% to to 30% did not.[11,12]

What underlies the failures? Some cases have diagnostic errors, and the patient does not have Cushing's disease. In other patients, those with Cushing's disease but unsuccessful surgery, the tumor is too small to find at surgery or incomplete tumor removal occurs, often because of tumor invasion of the surrounding structures.

I will not attempt to summarize all aspects of Cushing's disease in this brief report but will focus on certain aspects of it that seem to be particularly pertinent for neurosurgeons and on elements that I have learned from a personal experience of operating on $>$ 1100 patients with Cushing's disease.

SURGICAL REMOVAL OF THE ADENOMA

The first is the strategy of consistent and complete removal of the tumor. Almost all of our focus in pituitary surgery for the past 30 years has been how to get to the sella, not how to remove the tumor. That is, all our focus has been on the foreplay. In my experience over the past 25 years, a specific technique for tumor removal has been rewarding: the use of the histological pseudocapsule as a surgical capsule in removal of pituitary tumors of all types.[13,14]

Pituitary tumors are clonal tumors.[15] They originate from a single cell, and as they grow, they compress the pituitary gland adjacent to the tumor. By the time a tumor becomes large enough for us to detect it on MRI or to identify it at surgery, it has compressed the pituitary gland at its margin to the extent that it creates a thin tissue envelope, a histological pseudocapsule, a distinct tissue envelope surrounding it that permits its identification and removal by working around the edge of the pseudocapsule, using it as a surgical capsule, as shown in Figure 2. Investigation of the edge of that tumor with histology demonstrates a strong, multilayered, reticulin envelope around the edge of the tumor.

There are certain advantages that derive from using that tissue envelope, the histological pseudocapsule, as a surgical capsule: It can be used to identify small adenomas, adenomas that would otherwise not be apparent, and by following the edge of the pseudocapsule as a surgical capsule around the boundary of the tumor, we can use it as a distinct tissue plane between it and the surrounding compressed pituitary gland to identify sites of invasion of the pituitary capsule (the surface of the pituitary) and the surrounding dura. In larger tumors, I use it to aid in the preservation of the normal pituitary and to achieve complete tumor removal. Figures 3 and 4 display techniques for using the histological pseudocapsule as a surgical capsule in the removal of microadenomas and macroadenomas. I am particularly disciplined in maintaining the tissue planes during the surgery, initially in opening the dura and separating the dura from the capsule of the pituitary gland, first anteriorly and then laterally. After the pituitary is exposed, rather than making an incision directly into the tumor, as is generally done, I make an incision through the capsule of the pituitary at the margin of the tumor so that a thin layer of the normal gland is breached before reaching the pseudocapsule; this permits easy identification of the interface between the gland and the margin of the tumor. Further dissection around the margin of the tumor becomes almost effortless because of the concentric nature of the tissue planes at the tumor margin. By diligently using the tissue plane, exposure and exploration of the sella and tumor removal can be done bloodlessly and without coagulation. If a tumor is removed in this manner and is stained for adrenocorticotrophic hormone (ACTH) immunohistochemistry, it is evident that, despite the fact that the tissue capsule is strong during the surgery, it is often very thin but contains the entire tumor.

The same technique can be used to remove larger tumors (Figure 4). With larger tumors, one begins by working around the edge of the tumor using the pseudocapsule as a surgical plane and then removing tumor from within to reduce the mass of the tumor but still retaining 2 to to 3 mm of tumor at the edge of the tumor, adjacent to the surgical capsule, and then going back to the dissection plane to separate the tumor margin from the surrounding normal gland, remove the tumor, and leave the pituitary in place.

TUMORS IN UNUSUAL LOCATIONS

This feature occurs far more often in Cushing's disease than with other types of pituitary tumors. In most patients with ectopic parasellar adenomas, there is an associated partially

empty sella syndrome, which, in the face of an otherwise normal pituitary MRI, is a clue to carefully assess the parasellar structures such as the sphenoid mucosa, cavernous sinuses, and pituitary stalk for a tumor that arose outside the anterior lobe.[16,17] Figure 5 demonstrates the MRI and computed tomography results in a patient with an ectopic, parasellar ACTH-producing tumor in the sphenoid mucosa. These tumors may also arise above the pituitary in the pituitary stalk (Figure 6 demonstrates a microadenoma in the stalk, just beneath the optic chiasm) or in the wall of the cavernous sinus just lateral to the lateral margin of the pituitary gland. The approach that I have used to remove a series of ACTH-producing tumors in the pituitary stalk is depicted in Figure 7. These adenomas can often, but not always, be removed with preservation of pituitary function.

PATIENTS WITH NO ADENOMA VISIBLE ON MRI

Importance of the Endocrine Tests for Establishing the Presence of Cushing's Syndrome and to Establish the Cause of the Cushing's Syndrome

How should we manage the patient who presents with the clinical features of Cushing's syndrome and negative pituitary MRI (Figure 1)? Because during surgical exploration of the pituitary it is challenging to find an ACTH-producing adenoma if the patient does not have one, the initial tasks in these patients is to establish that the patient has Cushing's syndrome, the general syndrome of excess cortisol secretion, and then to demonstrate Cushing's disease and not one of the

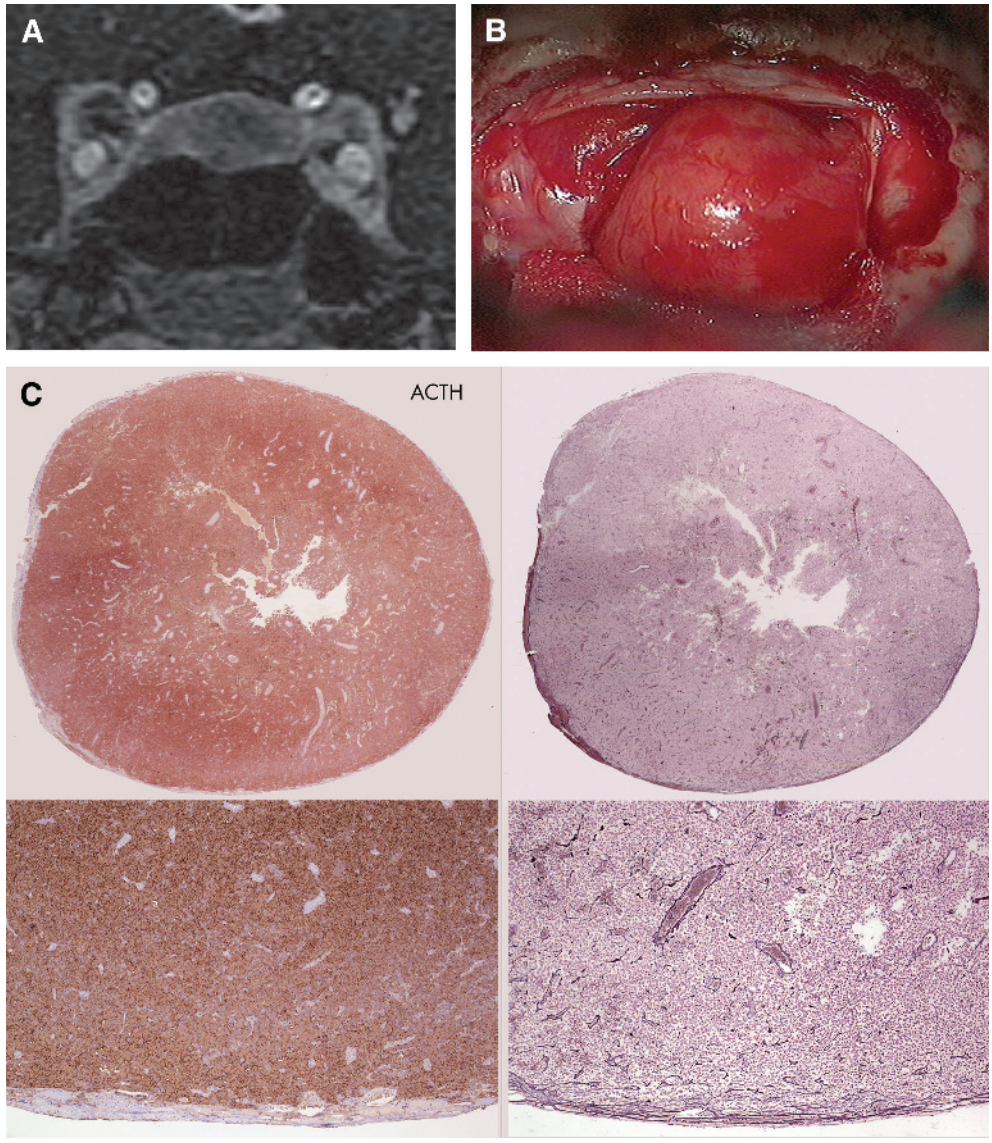

FIGURE 2. The use of the histological pseudocapsule as a surgical capsule. A, coronal T1 MRI after contrast demonstrating an intrasellar macroadenoma filling the left 80% of the sella in a patient with Cushing's disease. B, the adenoma has been removed by using the histological pseudocapsule as a surgical capsule. Operative photographs show the adenoma after dissection of its margin from the surrounding normal pituitary gland. The adenoma lies within the left side of the gland. C, adrenocorticotrophic hormone (ACTH; left) and reticulin (right) immunohistology of the intact specimen demonstrates that the pseudocapsule of the pituitary adenoma is intact over the adenoma. When the margin of the intact adenoma is examined in detail (along the bottom edge of the specimen in the bottom images; × 5), the layers of compressed reticulin surrounding the margin of the tumor are obvious. Despite the thin reticulin envelope containing this tumor, it was strong enough to remain intact during dissection, permitting complete removal of the tumor as an intact specimen.

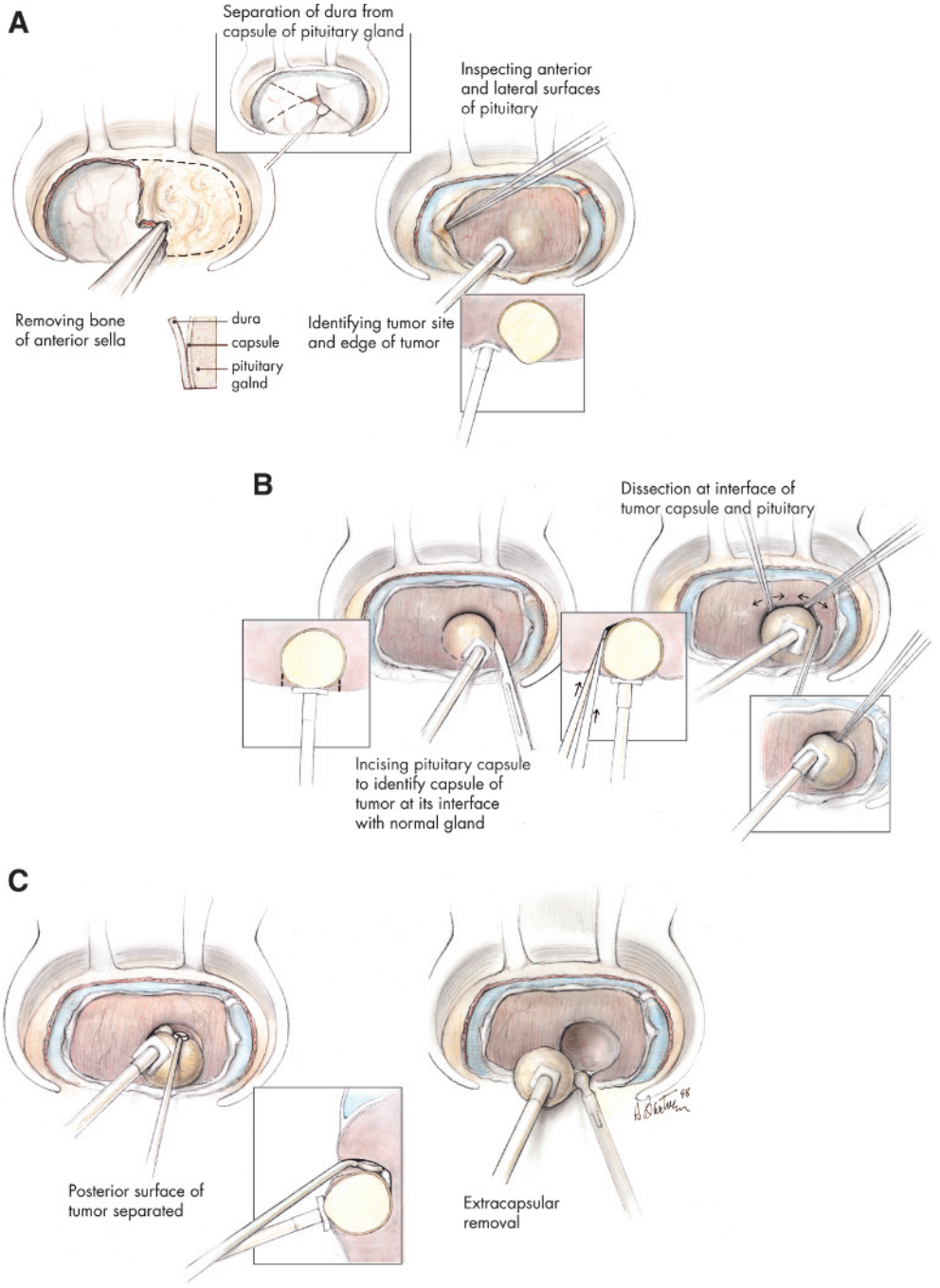

FIGURE 3. A, schematic drawings showing exposure of the pituitary. The initial opening of the anterior face of the sella turcica is performed using a drill with a 3- to 4-mm burr. A 2-mm Kerrison rongeur with a thin distal lip (0.75 mm) is used to remove the remaining thin layer of bone of the anterior sella face in small increments. These small pieces of bone can be flushed away with a brief pulse of saline irrigation, which is performed by the assistant, and suctioned away, permitting removal of the pieces without removing instruments from the working region. The bone is removed laterally until at least 2 mm of the most medial aspect of each cavernous sinus is visible. Superiorly bone removal extends to the tuberculum sellae. Inferiorly, a disk dissector is used to separate the dura gently from the bone of the sella floor after the anterior face of the sella has been removed. The sella floor is then removed with a small pituitary rongeur. Oozing bone margins are covered with a thin layer of bone wax and compressed into the bone interstices by using manipulation of a cotton pledget with the forceps tips. Because of the very low pressure in the cavernous sinus and the smaller dural veins draining into it, the same technique or placement of small pieces of Gelfoam soaked in thrombin can be used successfully for any site that slowly oozes blood from the layer between the dura and bone at the margins of the bone removal. At this stage, the operative field should be bloodless and should expose the entire anterior sella dura and most of the inferior dura covering the pituitary. Much of the success of the surgery depends on achieving a wide and completely bloodless exposure. Inspection of the dura reveals any region of invasion of the anterior or inferior dura, and in cases of small tumors that reach the anterior surface of the pituitary gland, careful examination of the dural surface may provide clues to the site of the tumor such as a slight local protuberance or a focal region of dark or light color. Because coagulation of the dura tends to glue it to the underlying pituitary capsule (impeding the capacity to open the dura sharply while leaving the pituitary capsule intact) and because it produces a region of white discoloration of the pituitary capsule and the contiguous region of the pituitary gland immediately beneath it (discoloration that may be misleading when searching for a small microadenoma), coagulation of the anterior or inferior dura is avoided during the exposure. All suction from this point is through a 0.5-in square cotton pledget onto which the suction tip is placed close to the margin. The dura is opened using a No. 15 scalpel with care to take the incision completely through the dura without entering the capsule of the pituitary gland. To achieve the widest available exposure, the superior margins of the incisions are extended laterally to reach the interface of the circular sinus and the medial margin of the cavernous sinus (upper inset).

other potential causes of Cushing's syndrome such as ectopic ACTH secretion or an adrenal adenoma.

About 85% of patients who develop Cushing's syndrome have pituitary adenomas. Various endocrine tests have been designed over the past 5 decades to distinguish among these entities (Table).

An important feature of all the tests for the differential diagnosis of Cushing's syndrome is that their accuracy depends on the normal hypothalamic-pituitary-adrenal (HPA) axis being fully suppressed by chronic excess cortisol secretion. Thus, we depend on our understanding of the normal HPA axis and its regulation to understand the pathophysiology of the various causes of Cushing's syndrome and to design and understand the tests used for diagnostic testing.

Normal Regulation of the HPA Axis

For normal regulation of ACTH and cortisol secretion, corticotrophin-releasing hormone (CRH) from hypothalamic neurons stimulates ACTH secretion from the pituitary corticotroph, which enters the bloodstream and simulates the adrenal cortex to produce and secrete cortisol (Figure 8).[18] This system is tightly regulated by the sensitive negative feedback of cortisol to suppress CRH production and secretion by the hypothalamic neuron and ACTH production and secretion from the pituitary corticotroph. All the endocrine tests for the differential diagnosis of Cushing's syndrome (Table), including inferior petrosal sinus sampling, depend on suppression of the HPA axis for their accuracy.

Bilateral Simultaneous Sampling of the Inferior Petrosal Sinuses

The hazard with the conventional endocrine tests is that they, when used alone, have a diagnostic accuracy of only about 85%. Because the individual endocrine tests are not as accurate as we would like, we can use combinations of tests, and if their results consistently point to a specific diagnosis, we can feel more secure in the diagnosis. Because of the limitations of the diagnostic accuracy of the conventional endocrine tests, several years ago, my colleagues and I began to investigate the simultaneous placement of catheters in both inferior petrosal sinuses (Figure 9)[19] combined with CRH infusion for the differential diagnosis of Cushing's

FIGURE 3 (continued).
The cavernous sinus is often intentionally entered along the superior and lateral margin of the exposure, where the lateral aspect of the circular sinus meets the medial aspect of the superior portion of the cavernous sinus. Low-pressure venous bleeding from this opening is controlled by simply plugging the opening with a small piece of Gelfoam moistened in thrombin. To achieve a wide exposure laterally and inferiorly, the medial inferior region of the cavernous sinus is frequently opened during the lateral-most extent of the incision, and bleeding is controlled in a similar fashion. The dura is gently and cleanly separated from the pituitary capsule by using a disk dissector in the tissue plane between these layers. This exposes the entire anterior surface of the pituitary gland with an intact pituitary capsule in a bloodless field. Similar to the pia mater, the capsule of the pituitary gland (lower inset) is a strong layer despite its translucent nature, and even though it is visible histologically, like the pia mater, the capsule is invisible to the surgeon. It must always be cut sharply; blunt dissection will not open it and will only transfer pressure to the interior of the gland and to the tumor, potentially spilling the partially liquefied center of the tumor prematurely. B and C, use of the surgical capsule for selective excision of small adenomas that are visible on MRI. When dealing with tumors within the gland that are visible on MRI, a curvilinear incision is made through the pituitary capsule just beyond the point at which the most superficial dome of the tumor reaches, or comes closest to reaching, the surface of the gland (B, left). Thus, this initial incision is not made directly into the tumor, as is common practice. This permits a thin layer of normal gland to be passed through before reaching the surgical capsule of the adenoma (left inset), allowing easy identification of the surgical capsule and the creation of a surgical plane of dissection at the margin of the tumor, at the interface of the normal gland and the surgical capsule of the adenoma. This interface between the adenoma and gland is further defined using the tips of the bipolar forceps in a series of movements parallel to the surface of the adenoma and in the crevice between the gland and adenoma (B, right and center and right insets). If the correct tissue plane is used, the dissection is unimpeded, and the gray-white surface of the adenoma is spherical and smooth. After this interface has been clearly defined, gentle dissection of the interface between the adenoma and gland is continued following the curvilinear margin of the adenoma, with further incisions in the capsule of the pituitary gland just beyond the tumor margin to release tension on the tumor as the dissection proceeds. A small Hardy sucker (2-mm tip) on the margin of a cotton pad is used to provide separation of the interface between the gland and the adenoma for dissection and for sponging the small amount of bleeding out of the field of view. Small pieces of Gelfoam soaked in thrombin help preserve the surgical space along the dissected margins while dissection takes place at other sites around the tumor margin (not shown here). After the most superficial portion of the tumor has been defined circumferentially, the deeper adenoma margins are defined and dissected in a similar fashion (C); the posterior margin of the adenoma often requires dissection using a disk dissector and a small and/or medium ring curette (C, left and center inset). This is performed gently; very little pressure is required if the correct tissue plane is being used, and most of the limited pressure that is applied is directed more toward the gland than the adenoma. After the margins of the tumor have been completely dissected, to prevent rupture of the tumor, the last remaining connection between the pseudocapsule of the specimen and the pituitary capsule is grasped with a small cup forceps, and the tumor is removed (C, right). In cases of tumors $\leq$ 8 to 10 mm in diameter, the entire tumor can usually be shelled out of its bed in the anterior lobe as an intact specimen. Successful and complete removal leaves a smoothly lined hemispherical tissue void in the anterior lobe. From Oldfield EH, Vortmeyer AO. Development of a histological pseudocapsule and its use as a surgical capsule in the excision of pituitary tumors. *J Neurosurg*. 2006;104(1):7-19.[14] Printed with permission.

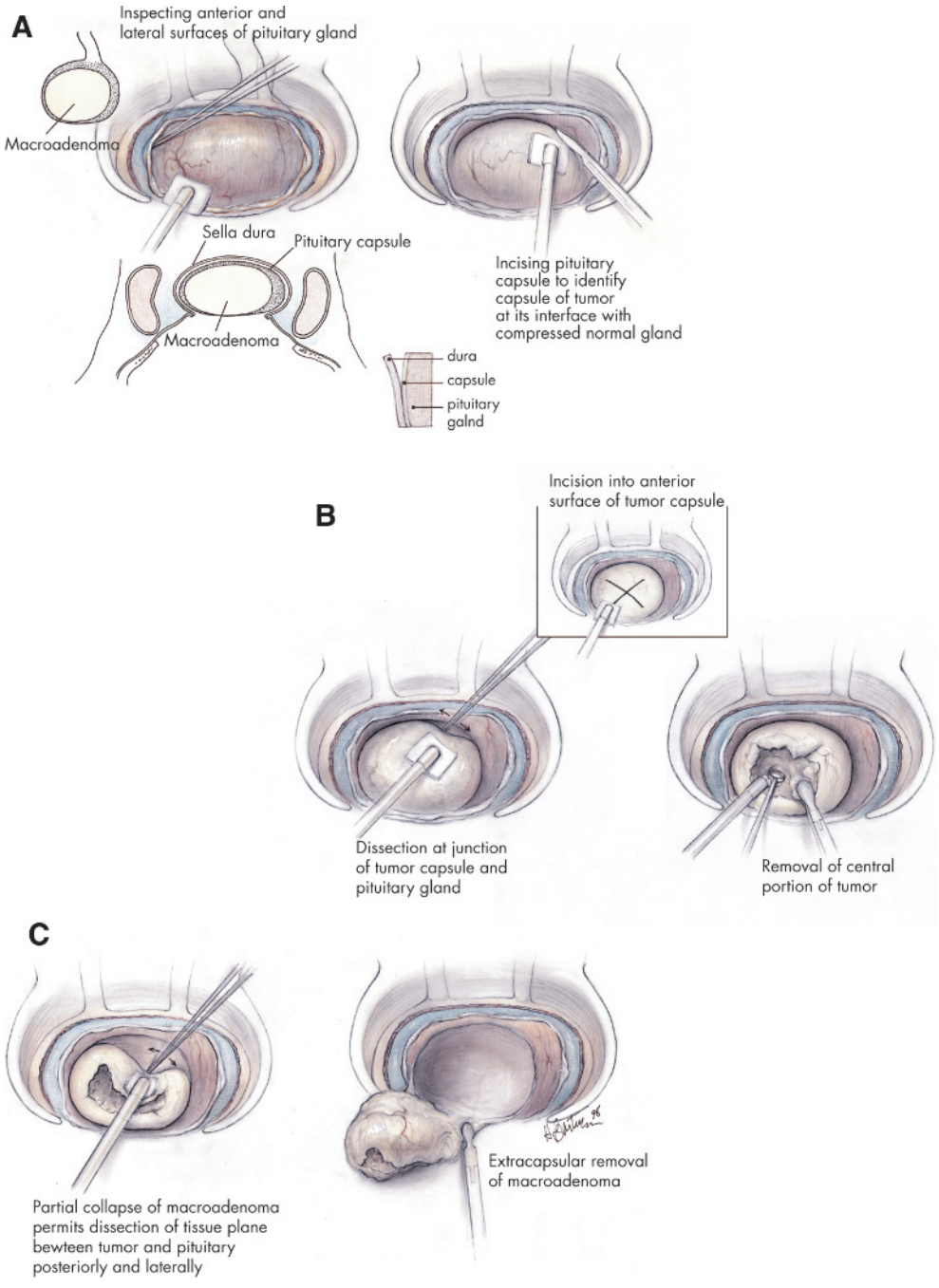

FIGURE 4. Macroadenomas with expansion of sellar contents and/or suprasellar extension. Almost all macroadenomas, regardless of their size, are associated with a preserved but compressed and displaced anterior pituitary gland at some location along their margin. The compressed anterior lobe can be identified, separated from the tumor by the use of the surgical capsule of the macroadenoma, and preserved during surgery. This is initially accomplished by preserving the capsule of the pituitary gland during the dural opening (A). After the capsule of the anterior lobe has been separated from the dura, a very superficial—a fraction of a millimeter—horizontal incision is made just through the pituitary capsule by using the belly of a No. 15 scalpel (B, right); the site of this incision is usually approximately 2 to 3 mm below the most superior exposure of the intradural sellar contents. This incision is made so that its depth is just to the edge of the surgical capsule of the macroadenoma, permitting the margin of the adenoma to be defined. Dissection, made with the tips of the bipolar forceps (B) as described in the legend for Figure 5, further separates the gland from the adenoma, and as the dissection proceeds, more of the normal gland becomes apparent. Further sharp incision of the pituitary capsule is performed to stay just beyond the margin of the dissected interface, between the compressed gland and the surgical capsule of the macroadenoma. In this fashion, the most superficial portion of the macroadenoma is separated from the compressed gland (A and B). When this surgical plane has been carried to a depth of 3 to 4 mm along the superior, lateral, and inferior edges (B, left) of the exposed tumor (usually in that sequence), the anterior face of the adenoma is incised and the central portion of the tumor is removed (B, right). This is performed to reduce the mass of the tumor and to provide the space needed to continue the circumferential dissection of the gland-tumor interface by using the tips of the bipolar forceps and disk dissectors to deeper levels. It is important not to remove too much of the central portion of the tumor during the debulking because the outer layer of the macroadenoma (the shell of the tumor) is easier to work with if a 2- to 3-mm thickness of its capsule is left intact. This leaves enough thickness of the capsule to provide structure to the tumor margin, which enhances the ease of further dissection (C). It is often necessary to dissect the posterior one-third of the tumor margin gently by using ring curettes with gentle pressure, as described in the legend for Figure 5, so as not to rupture the surgical capsule of the macroadenoma during its excision. From Oldfield EH, Vortmeyer AO. Development of a histological pseudocapsule and its use as a surgical capsule in the excision of pituitary tumors. *J Neurosurg.* 2006;104(1):7-19.[14] Printed with permission.

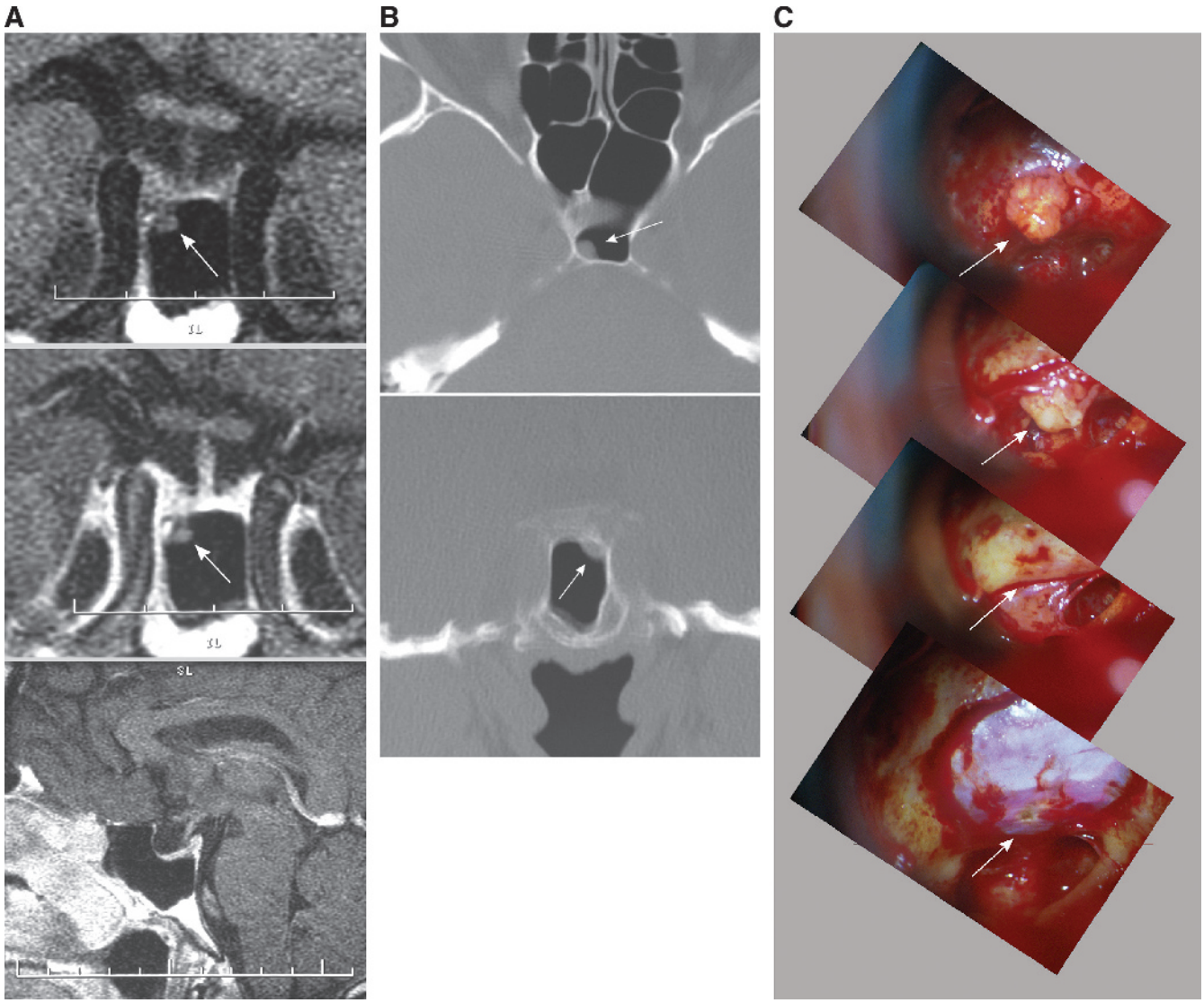

FIGURE 5. A, pituitary MRI before (upper) and after (middle, bottom) contrast enhancement. Note the adenoma in the sphenoid mucosa (arrows) and that the ectopic adenoma is associated with an empty sella syndrome (bottom). B, computed tomography shows that the bone of the sella floor is intact, as is also seen at surgery. C, the series of operative images, taken in sequence from top to bottom during exposure and removal of the tumor, show the intact tumor in the sphenoid mucosa (top 2 images), that the tumor was outside the bone (the sella face and floor are shown intact in the third image from the top), and that the dura is also intact in that region of the sella (bottom).

syndrome.[13,14] What we found in a large series of patients was what we expected to find, ie, that patients with Cushing's disease have a higher ACTH concentration in at least 1 inferior petrosal sinus compared with the peripheral blood (Figure 9B, left), whereas patients with ectopic ACTH secretion do not (Figure 9B, right). By using the maximal ratios before or after CRH, the test has a very high diagnostic accuracy to separate patients with Cushing's disease with those from ectopic ACTH secretion (Figure 9C).

We also thought at one time that we could use this test to lateralize where the tumor was in patients with Cushing's disease; in fact, that turned out not to be as accurate as we thought it would be, so now we tend to use the test mainly for the differential diagnosis and only use it when individual patients have results that conflict with the other endocrine testing or have a negative MRI. Its utility for localizing the side of the pituitary containing an adenoma is limited.

The patient must have demonstration of excess cortisol production before using the tests for the differential diagnosis of Cushing's syndrome. Today, in the midst of an epidemic of obesity, we must keep in mind that if we perform any of these tests for the differential diagnosis of Cushing's syndrome

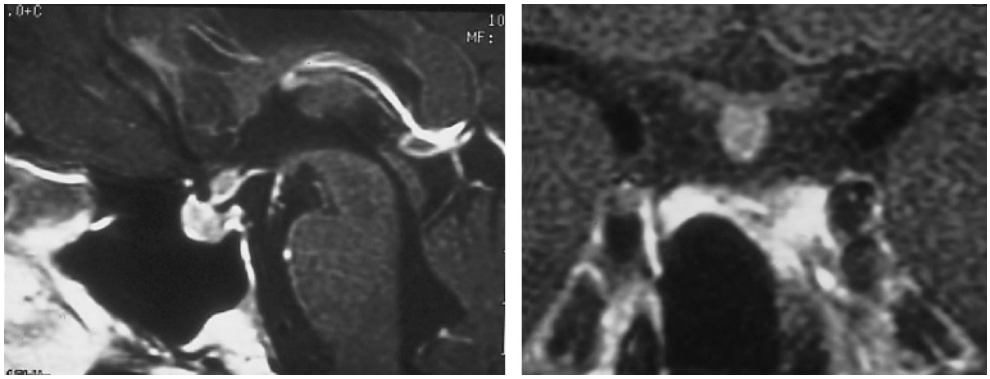

FIGURE 6. Magnetic resonance T1-weighted images revealing a 7-mm adenoma arising high in the pituitary stalk, just beneath the optic chiasm. Note enhancement of the anterior lobe and stalk, but not the tumor. From Mason RB, Nieman LK, Doppman JL, Oldfield EH. Selective excision of adenomas originating in or extending into the pituitary stalk with preservation of pituitary function. *J Neurosurg*. 1997;87(3):343-351.[17] Printed with permission.

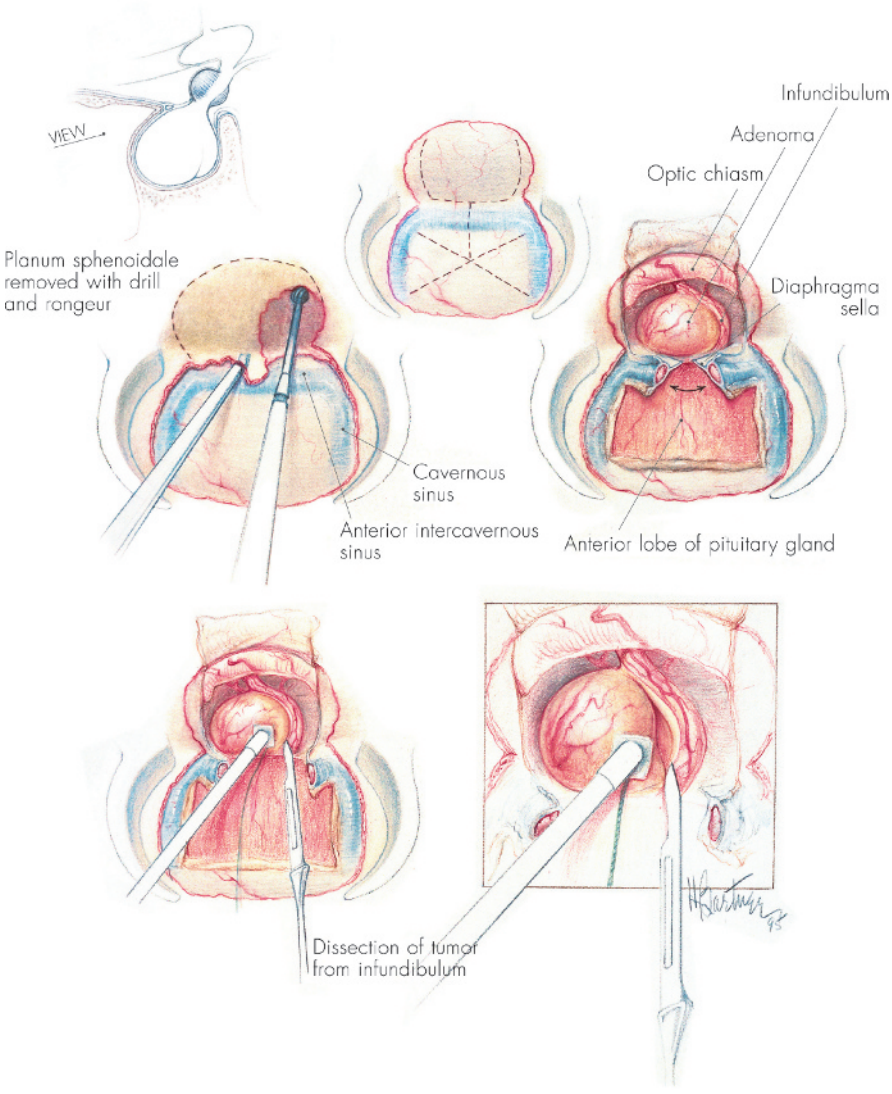

FIGURE 7. Drawings depicting the routine wide exposure of the anterior surface of the sella and bone removal to expose the medial portion of the cavernous sinus bilaterally. In patients in whom MRI indicated stalk involvement, the posterior portion of the planum sphenoidale (the posterior 4-6 mm) was removed by first drilling with a rough diamond burr until the plate of bone was paper thin and then using a 2-mm-thin-footplate cervical Kerrison rongeur. Removal of the planum sphenoidale aided access to the suprasellar cistern, pituitary stalk, and superior surface of the gland. The dura mater covering the anterior pituitary surface was opened widely. Bilateral parasagittal incisions were made 8 to 10 mm apart in the dura overlying the planum sphenoidale. A transverse incision just above the anterior portion of the circular sinus was then used to connect the parasagittal incisions. The resulting dural flap was opened posteriorly while initially preserving the intact arachnoid. After entering the suprasellar cistern, the superior hypophyseal artery was identified and care was taken not to injure it. The exposed diaphragma sella was incised in the midline, in an anteroposterior direction, to reach the stalk and the supradiaphragmatic tumor. A small piece of Gelfoam or cottonoid was placed superiorly in the subarachnoid space to prevent passage of blood into the cerebrospinal fluid. Characteristic vertical striations produced by the vertical course of the surface blood vessels permitted identification of the stalk. A sharp incision was made in the piaarachnoid with a No. 11 or 15 scalpel at the junction of the capsule of the tumor with the pituitary stalk and, when appropriate, in the superior surface of the anterior lobe at the margin of the adenoma. The adenoma was then resected using standard microsurgical techniques. From Mason RB, Nieman LK, Doppman JL, Oldfield EH. Selective excision of adenomas originating in or extending into the pituitary stalk with preservation of pituitary function. *J Neurosurg*. 1997;87(3):343-351.[17] Printed with permission.

TABLE. Endocrine Testing in Cushing's Syndrome

Established diagnosis of Cushing's syndrome
A 24-h urine collection for free cortisol measurement
Low-dose overnight dexamethasone suppression test
Nocturnal salivary cortisol measurement
Differential diagnosis of Cushing's syndrome
High-dose overnight dexamethasone suppression test
Corticotrophin-releasing hormone stimulation test
Bilateral simultaneous inferior petrosal sinus sampling
Combinations of tests

(listed in the Table) in a patient who does not have sustained excess cortisol production sufficient to suppress the HPA axis, the results will consistently yield a result that indicates Cushing's disease. Thus, if we evaluate a patient with obesity who does not have Cushing's syndrome with these tests, they will all suggest a diagnosis of Cushing's disease, and we are at risk of taking the patient to surgery, not finding a tumor, removing all or a portion of the pituitary, and considering either sellar irradiation therapy or bilateral adrenalectomy, all in a patient who did not have Cushing's syndrome to begin with. Thus, the necessary caution is to keep in mind that the logical use of all the tests for the differential diagnosis of the clinical expression of chronic hypercortisolism from any cause, Cushing's syndrome, depends on complete suppression

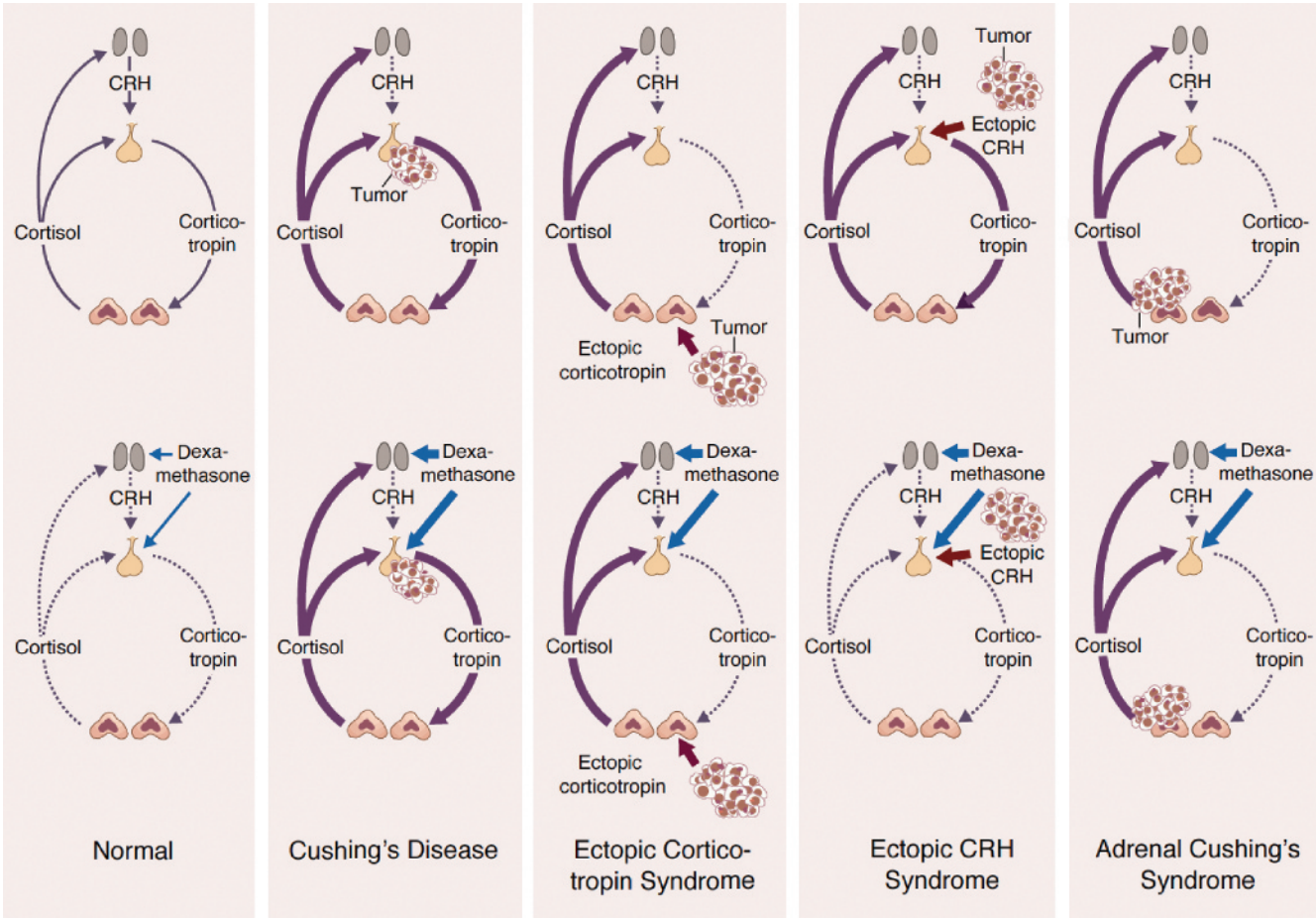

FIGURE 8. Physiological and pathophysiological features of the hypothalamic-pituitary-adrenal axis in normal subjects and patients with Cushing's syndrome (top) and the effect of dexamethasone (bottom). Stimulation of the hypothalamus by other central nervous system centers such as the locus caeruleus regulates the secretion of corticotrophin-releasing hormone (CRH); corticotropin stimulates adrenal secretion of cortisol; and cortisol inhibits the secretion of both CRH and corticotropin. Adrenal (ie, corticotropin-independent) Cushing's syndrome is caused by adrenal tumors and corticotropin-independent bilateral micronodular and macronodular adrenal hyperplasia. Low doses of dexamethasone are shown by thin blue arrows; high doses, by thick blue arrows. Normal hormone secretion is shown by thin purple lines; suppressed secretion, by dotted purple lines; and hypersecretion, by thick purple lines. From Orth DN. Cushing's syndrome. *N Engl J Med*. 1995;332(12):791-803.[18] Printed with permission.

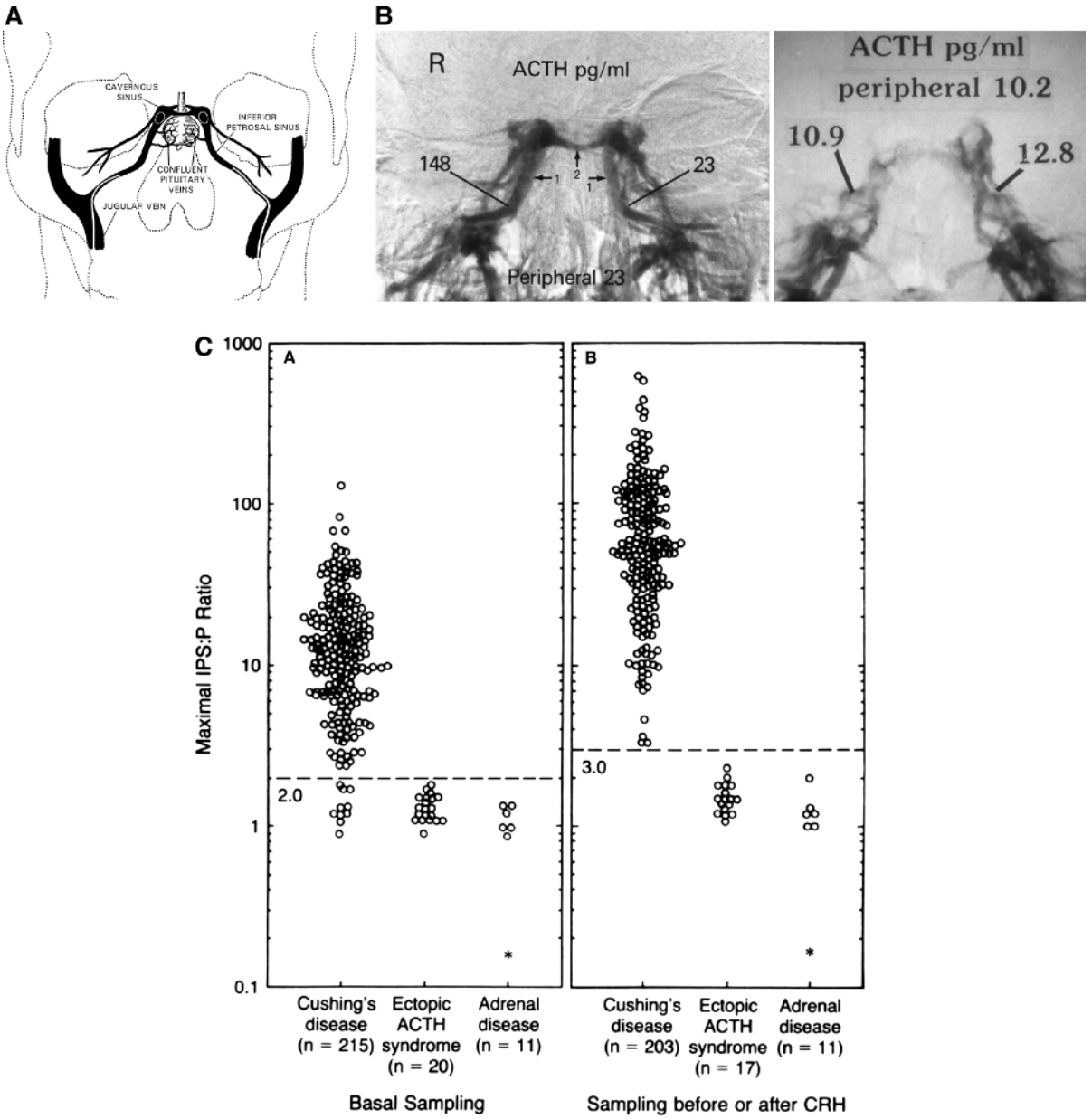

FIGURE 9. A, anatomy and catheter placement in bilateral simultaneous blood sampling of the inferior petrosal sinuses. Confluent pituitary veins empty laterally into the cavernous sinuses, which drain into the inferior petrosal sinuses. B, venous sampling during inferior petrosal venous sampling with adrenocorticotrophic hormone (ACTH) levels from a patient with Cushing's disease (left) and a patient with a bronchial carcinoid and ectopic ACTH secretion (right). From Oldfield EH, Chrousos GP, Schulte HM, et al. Preoperative lateralization of ACTH-secreting microadenomas by bilateral and simultaneous inferior petrosal sinus sampling. *New Engl J Med*. 1985;312:100-103 with permission. C, bilateral inferior petrosal vein sampling in the differential diagnosis of Cushing's syndrome. Maximum ratio of ACTH concentration from one of the inferior petrosal sinuses to the simultaneous peripheral venous (IPS:P) ACTH concentration in patients with Cushing's syndrome in basal samples (left) and in basal and corticotrophin-releasing hormone (CRH)–stimulated samples(right). During basal sampling, the maximum IPS:P ACTH ratio was $\geq$ 2.0 in 205 of 215 patients with confirmed Cushing's disease but was $<$ 2.0 in all patients with ectopic ACTH syndrome or primary adrenal disease. All patients with Cushing's disease who received CRH had maximum IPS:P ACTH ratios of $\geq$ 3.0, whereas all patients with ectopic ACTH syndrome had IPS:P ratios of $<$ 3.0. The asterisks represent 5 patients with primary adrenal disease in whom ACTH was undetectable in the peripheral blood before and after CRH administration. From Oldfield EH, Doppman JL, Nieman LK, et al. Bilateral inferior petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. *N Engl J Med*. 1991;325(13):897-905.[23] Printed with permission.

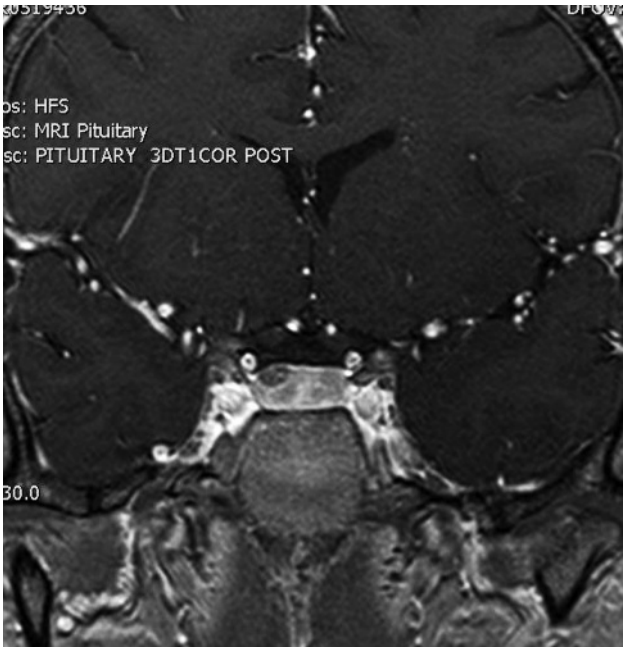

FIGURE 10. Pituitary spoiled gradient recalled acquisition (SPGR) MRI of a patient with pituitary microadenoma not visible on conventional MRI. Coronal postcontrast SPGR image of the pituitary demonstrates an abnormal area of diminished enhancement with respect to normal pituitary parenchyma in the superior and lateral margin of the anterior lobe on the patient's right (arrow). This abnormality represents an adrenocorticotrophic hormone (ACTH)–secreting adenoma, which was confirmed at surgery. Compare this image with the image in Figure 1, which was obtained in the same patient after contrast using conventional spin echo imaging.

of the normal pituitary-adrenal axis by excess cortisol production. We can avoid taking this potentially misleading path by insisting that the patient has been demonstrated to have Cushing's syndrome, established by elevated 24-hour urine-free cortisol measurements, low-dose overnight dexamethasone suppression, and/or nocturnal salivary cortisol measurements, before introducing the tests for differential diagnosis of a patient who has been shown to have Cushing's syndrome.

Enhanced MRI in Patients With Negative Conventional Pituitary MRI

In a patient with a diagnosis of Cushing's disease and a tumor so small that it cannot be detected with MRI, the challenge is finding the tumor; if the tumor can be identified and is contained within the capsule of the anterior lobe, it can almost always be completely removed, leading to cure. The resolution of a 1.5-T magnet may reveal tumors as small as 3 mm in diameter. The spoiled gradient recalled acquisition (SPGR) technique, used with 1-mm nonoverlapping slices, is more sensitive than the conventional spin-echo approach (sensitivity, 80% vs 49%; Figure 10).[20,24] Because MRI abnormalities typical of an adenoma occur in the pituitary gland in 10% of normal volunteers[22] and incidental adenomas are found in the pituitary gland in about 15% to to 20% of subjects in autopsy studies of patients without endocrine disorders,[5,6] the results of MRI scanning must be confirmed by endocrinological testing.

Surgical Management of Patients With Negative MRI

Despite the use of the best available MRI techniques, many patients still have a negative MRI, and we must locate and identify the adenoma during surgical exploration. We find the tumors in these patients by a systematic approach, initially exposing the pituitary widely and bloodlessly, providing visual inspection of the anterior and then the lateral surfaces of the gland from one side to the other and then, if no tumor is apparent by inspection of the surface, by a thorough search through the pituitary gland with multiple incisions. I have found the presence of a pseudocapsule to be the most reliable indicator of the site of a microadenoma imbedded in the pituitary gland (Figure 11).

What if a tumor cannot be found during surgical exploration? After inspecting the surface of the pituitary and then making a series of incisions in the gland and still not being able to find a tumor, the surgeon has to options of removing the entire gland (which eliminates Cushing's disease in about two-thirds of patients after a negative surgical exploration), removing half of the anterior lobe on the side of an ACTH gradient exposed during petrosal sinus sampling (which in my experience induces remission of Cushing's disease in about 75% of patients), or removing the lateral 25% from each side and then the bottom quarter, leaving about 25% of the gland attached to the stalk (which eliminates Cushing's disease in about 75% of patients). Because total hypophysectomy leads to lifelong panhypopituitarism and the other choices provide the same chance of success but do not submit the patient to about a 10% to to 20% risk of hypopituitarism, one of them, and it does not seem to make much difference in outcome between them, is a better choice.

PERSISTENT OR RECURRENT CUSHING'S DISEASE

Persistent or recurrent adenoma after previous surgery with excision of an adenoma is invariably located at, or immediately contiguous to, the site of the adenoma at the original surgery,[23] indicating that recurrence of Cushing's disease is from growth of residual cells left in situ at the original surgery and that, at repeat exploration, the site occupied by the original tumor should be the focus of the exploration.

Lateral dural invasion involving the wall of the cavernous sinus accounts for the great majority of patients who have

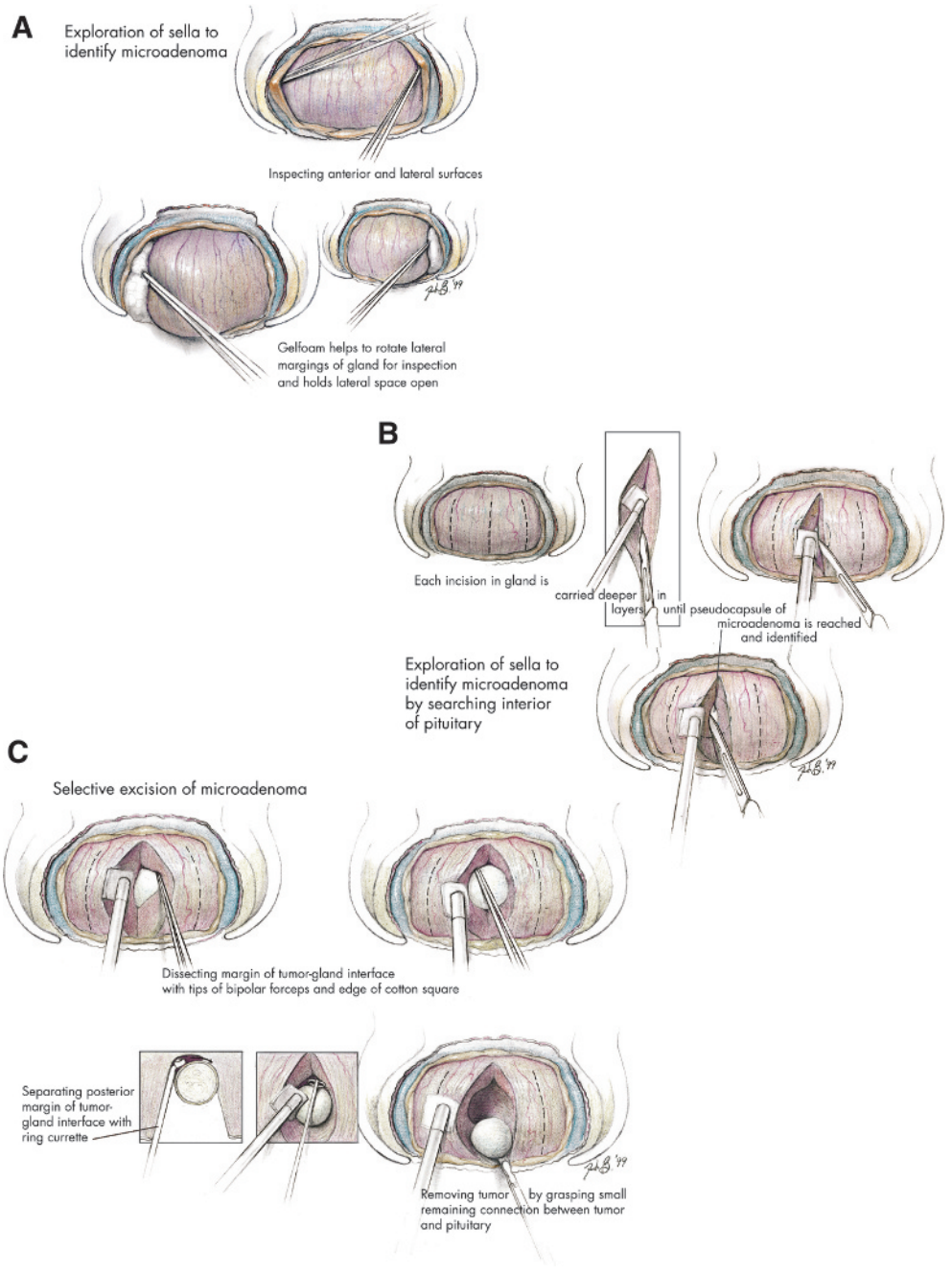

FIGURE 11. Exploration of the pituitary gland in patients with an endocrine-active adenoma whose imaging studies appear normal. The goal of the exploration is to find and identify the distinct encapsulated margin of the adenoma. Success depends on beginning with a widely exposed, bloodless surgical field (A). Coagulation of the anterior and inferior sella dura is avoided during the exposure and dural opening because it would produce a white area on the surface of the underlying gland that may falsely suggest the site of the adenoma. After widely opening the dura, which provides exposure of an intact pituitary capsule covering the anterior surface of the gland, and after exposure of the extreme lateral margins of the anterior surface, the surfaces are carefully inspected for regions of focal discoloration. The adenoma usually appears to be gray-blue or yellow-white and can be identified against the background of the anterior lobe surface, which is orange-pink. B, if no tumor is seen, the lateral surfaces of the anterior lobe are then inspected. For this, the lateral dural wall of the sella (the medial wall of the cavernous sinus) is separated from the pituitary capsule by gently passing a disk dissector between these 2 layers from top to bottom. The space produced provides room for dissection of the interface between the lateral pituitary capsule and the dural wall with the closed tips of a fine-tipped bipolar forceps (B). Dissection is initially superficial and then progresses in stages to deeper levels until the posterior sella has been reached. After these 2 tissues have been separated, small pieces of Gelfoam are packed into the intervening space to rotate the lateral surface anteriorly and to gently displace it medially into the surgeon's direct view. After both lateral surfaces are exposed and examined in this fashion, the inferior surface of the gland is separated from the dura. (This is the site at which these 2 layers, the surface of the pituitary and the dura mater, are most tenaciously attached to each other.) If a tumor can be identified from inspection of the surface, it is removed as described in the text and the legend for Figure 5. If no tumor is identified on inspection of the superficial gland, a series of vertical incisions is then made (B), each of which begins 1 to 2 mm below the superior edge of the pituitary exposure and is directed downward, initially to a depth of only approximately 1 mm and then in stages deeper through the anterior lobe until either the intermediate lobe or the glistening white anterior surface of the posterior lobe is reached. Because the pituitary blood supply and the delivery of hypothalamic trophic factors to the pituitary are oriented vertically, vertical incisions should be less likely to cause an infarction in a portion of the pituitary or to isolate the gland from its hypothalamic regulation. A distinct tissue capsule is the primary object of the search, with the intent of identifying the margin of the tumor before entering it and spilling its contents, by using the surgical capsule of the adenoma (B and C). When the surgical capsule of the adenoma is identified, the tumor is removed using dissection along the interface of the adenoma and the normal gland, as described in the legend for Figure 5 (A and B).

FIGURE 11 (continued).
In cases of tumors lying in the posterior portion of the anterior lobe, a 2-mm-wide slice of the anterior lobe may be removed to provide space for dissection and removal of the deep microadenoma (not shown). From Oldfield EH, Vortmeyer AO. Development of a histological pseudocapsule and its use as a surgical capsule in the excision of pituitary tumors. *J Neurosurg*. 2006;104(1):7-19.[14] Printed with permission.

persistent or recurrent Cushing's disease. In my own series of 68 patients with repeat surgery 44 ± 35 months after the initial surgery for persistent or recurrent Cushing's disease, the tumor was found at the same site or contiguous to the same site in all 43 patients in whom an adenoma had been identified at the initial surgery.[23] Dural invasion by an ACTH-producing tumor was identified during surgery in 42 of the 68 patients (62%) re-explored after prior surgery and recurrent or persistent Cushing's disease. In addition, 39 of these 42 invasive adenomas (93%) were located laterally and involved the cavernous sinus. Adenoma invasion of the dura mater was found in 31 of 57 microadenomas (54%) and in all 11 macroadenomas at repeat surgery. The presence of tumor was not detected at all in 28 of the 59 patients studied with MRI, and in none of these 59 patients was dural invasion evident on MRI. The results of this study established that recurrent and persistent Cushing's disease consistently results from residual tumor. At repeat surgery, the residual tumor can invariably be found at, or immediately contiguous to, the site at which the tumor was originally found. Unappreciated dural invasion with growth of residual tumor within the cavernous sinus dura, which frequently occurs without residual tumor or dural invasion being evident on MRIs and often goes unnoticed by the surgeon during surgery, is the basis of surgical failure in many patients with Cushing's disease.

It is worth considering what underlies that preferential involvement laterally into the medial wall of the cavernous sinus through the very thick multiple layers of reticulin covering the pituitary gland. One of the clues to this comes from some studies in the venous drainage of the pituitary by Wislocki in the 1930's.[22] He described lateral venous drainage of the pituitary gland by confluent pituitary veins that penetrate the pituitary capsule and the dura of the cavernous sinus at the same site, producing an anatomic route of least resistance for potential invasion. Cell biologists would have us believe that the intrinsic biology of the tumor accounts for this invasion. The findings summarized above suggest that it may occur most often because of anatomic, rather than biological, features.

SUMMARY

One of the rewards of studying Cushing's disease is that the understanding of the stages of these tumors provides insight into what happens during the evolution of all types of pituitary tumors. The evolution of the development of the pseudocapsule at the margin of small adenomas begins to occur at about 2 to 3 mm in diameter,[14] the minimum size at which we can identify them during surgical exploration. Certain advantages derive from removal of pituitary adenomas using the histological pseudocapsule as a surgical capsule and as a defined tissue plane.

Other unresolved issues need our focus over the next few years. Surgical success would be enhanced if we had more accurate ways of localizing the very smallest tumors, either before or during surgery, in patients with Cushing's disease and negative MRI. We also need better therapies for tumors that invade the cavernous sinus, and we need to understand the biological basis of invasion in patients who have truly invasive tumors. Finally, it would be rewarding to understand the molecular basis of the relative resistance to negative cortisol feedback characterizing these tumors and why it is linked to tumor formation. We still have much to do.

Disclosure

The author has no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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