SYMPOSIUM ON PITUITARY TUMORS—I

SURGICAL TREATMENT OF PITUITARY ADENOMAS*

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The surgical treatment of pituitary adenomas is one of the fascinating chapters in the history of neurosurgery, but the end is not yet for I can foresee the addition of postscripts possibly for some years to come. Beginning with the courageous, though unsuccessful attempt by Sir Victor Horsley, 1889 (he reported it only in 1906) to remove a pituitary tumor intracranially, in the next 10 to 20 years other pioneers in surgery whose names are legend assailed the pituitary gland from below through the nasal cavities and above through various intracranial approaches.

Transphenoidal Operation. With variations, the transphenoidal approach to pituitary tumors was favored by most until the 1930’s when it is obvious from the writings of those years that there was dissatisfaction with this approach and increasing interest and skill in the intracranial operation. In 1921 Cushing wrote: “It is certain that no one method is applicable for all conditions of pituitary tumor and that for some no satisfactory procedure has been devised. Speaking for myself, I find that I am conducting proportionately fewer operations than have transphenoidal operations.” After the next 10 years, during which time there was a gradual transition from the transphenoidal to the transfrontal operation, he (Cushing), in support of better visualization afforded by the intracranial exposure, wrote: “Whereas 37 per cent of the patients after trans-phenoidal operations and 42 per cent after transfrontal operations showed considerable or marked improvement in vision, only 9 per cent of the transphenoidal operations, in contrast to 21 per cent of transfrontal operations, were followed by restoration of the visual fields and acuity essentially to normal. It is in this respect that the transfrontal procedure definitely takes precedence over the other.”

In the years following, the intracranial approach has been more widely employed in surgery of pituitary adenomas, although both in America and elsewhere there have been advocates of the transphenoidal operation. No purpose would be served by an attempt to convert those who find favor in the transphenoidal over the intracranial operation and we should not lose sight of worth-while contributions that have come from such surgeons as Hirsch, whose monumental work extends over a period of half a century.

A few comments can be made in the present day on the comparative merits of the two operations. Some advocates of the transphenoidal operation make claim for its simplicity and harmlessness and for safety of the optic nerves; they minimize the risk of infection, spinal-fluid leaks, occasional difficulties in exposure of the sella, inadequacy in dealing with unanticipated suprasellar extensions or other tumors. One author, Deborsu, based on an experience of 80 transphenoidal operations for pituitary adenomas, reported at length on the difficulties. One remark in his résumé is revealing; he says once you have arrived at the floor of the
sella there are "no more difficulties, only dangers."

The indications for the transphenoidal operation have been listed as follows: (1) aged subjects in the 60's in whom the risk of intracranial operation is said to be great; (2) those on the verge of blindness in whom the possible manipulation of the optic nerves from the intracranial approach might add to the damage; and, (3) those with cystic or acutely hemorrhagic tumors or with downward extensions believed to be inaccessible from above.

My (B.S.R.) experience is limited to the intracranial operation, but I am unimpressed by claims of specific advantage of the transphenoidal operation and should view with apprehension any trend to revive more extensive use of it. There is little risk to life or of important complications from intracranial attack on pituitary adenomas that have not extended beyond the immediately adjacent confines of the sella and these tumors are outside the scope of a transphenoidal operation. As an old surgical principle, "adequate exposure" remains sound. Not only does the intracranial approach provide the means for viewing the tumor and its relation to the important intracranial structures, but by this approach everything can be accomplished that is possible by the transphenoidal operation. Horrax's\textsuperscript{2} evaluation indicates that by comparison the transphenoidal operation affords two to three times less protection against recurrence of chromophobe adenoma.

Radiation Therapy. Perhaps a more important consideration in the management of pituitary adenomas is the place of radiation therapy. For more or less 30 years many neurosurgeons looked upon the use of radiation therapy for chromophobe adenomas with uncertainty, if not with actual reluctance. There can be no doubt now that a tumor dosage in the neighborhood of 4,000 r will sometimes obviate the need for surgery\textsuperscript{8} and it seems likely that a similar dosage given after surgical resection of the adenoma will provide some protection against recurrent growth of the tumor.\textsuperscript{9} There is doubt that postoperative irradiation facilitates the recovery of vision if it has been possible to perform an adequate operation.

The popularization of radiation therapy in recent years has posed several problems, not the least of which has been its misuse, principally by those who are inexperienced or uninformed and who believe operation is dangerous and unnecessary. It is not an unique experience to have encountered patients whose vision, already seriously damaged before treatment was initiated, failed to improve or became worse with radiation and who had been led to believe surgery could offer nothing better.

With the advent of more widespread use of trial treatment by radiation the neurosurgeon must be aware of an additional responsibility. He should have a knowledge of the patient's progress during and after treatment, even if not always directly in charge of necessary frequent observations. He must develop some knowledge and conviction about when it is appropriate to interrupt or follow irradiation by operation and must not be guilty of accepting mediocre improvement or uncertain protection of vision as a compromise for operation.

A brief case report will serve to illustrate a few points.

A 40-year-old physician engaged in research had for several years been receiving replacement treatment for unexplained hypothyroidism and hypogonadism. The first suspicion of a pituitary adenoma followed the discovery of bitemporal hemianopsia after he was nearly run down by an unseen car. When the diagnosis was made, a tally of the many medical opinions showed a majority favoring radiation therapy. The treatment was given in two series (totaling 3,800 r, tumor dosage) over a period of 4 months and during this time weekly visual tests were performed (B.S.R.). Fig. 1 shows selection from these tests which graphically illustrate the transient reduction of vision occurring with each series of treatments. On termination of the treatment his vision was about the same as it had been before. Some of his advisors believed the visual changes irreversible, but for the patient his vision was not useful since his work depended on the use of a microscope. Prompt improvement followed operation.

The technique of radiation treatment currently recommended is different from that

Note the temporary reduction in visual acuity and perimetry during periods of radiation treatment (B & D) and the reduction in visual fields after completion of radiation treatment (compare E with A).

The final chart F shows the quick improvement that followed surgical removal of the adenoma (6 months' interval between A & F).

employed in this patient, but the tumor dosage is the same and certain points in question are the same. These points one must reconcile and they include the following: What degree of visual impairment makes it unsafe or undesirable to employ trial radiation therapy; is some degree of worsening of vision during therapy to be regarded as transient and if so, how much time may safely pass before interrupting the therapy and resorting to surgery; if vision does not improve after therapy, can it ever justifiably be assumed that operation would not accomplish more; and, how long is it appropriate to wait for hoped-for improvement in vision after termination of therapy?

Then, too, there is the disconcerting possibility of a mistaken diagnosis and the undesirable weeks of delay in operation on an aneurysm, a meningioma or craniopharyngioma, imposed by a needless trial of radiation in such cases. Should pneumoencephalography or angiography or both be employed before subjecting a patient to radiation therapy? Certainly, they are sometimes of advantage before operation and the use of these tests would obviate the ill-advised trial of radiation therapy for an adenoma with large extrasellar extension.

Transfrontal Operation. Although the op-
operative mortality following transfrontal operation for pituitary adenomas was reduced to 2.4 per cent in the last 10 years of Cushing's series, few seemed able to match this accomplishment in the years that followed. However, there is no reason why we cannot now and in the future expect a reduced operative mortality and morbidity as a result of early diagnosis and of certain refinements and aids in surgical technique, supplemented by the use of modern replacement therapy for endocrine deficiencies and for electrolyte imbalances.

In the preoperative evaluation of the patient with a pituitary adenoma, careful study of vision, particularly the fields of vision, continues to be the most important and should never be delegated to an inexperienced or disinterested co-worker. Next in order comes detection of neurological symptoms or signs such as mental changes, extraocular palsies, evidence of temporal-lobe involvement, long-tract signs and increased intracranial pressure, all of which give clues to possible large extrasellar extensions of the tumor or to other tumors or aneurysms which by their effect on the optic nerves and chiasma may simulate a pituitary tumor.

A study of the radiologic appearance of the sella and adjacent regions may reveal, in addition to an enlarged sella, the presence of a meningioma of the tuberculum sellae or sphenoid ridge, the peculiar configuration produced by a chiasmal or optic-nerve glioma, a calcified suprasellar cyst (craniopharyngioma) or certain other rarer calcified or bone-destroying tumors. The size of the sella and degree of destruction of its bony confines caused by a pituitary adenoma provide the surgeon with some assurance of landmarks when carrying out the operation. But the limitation of exact interpretation of roentgenograms of this region is common knowledge.

Fractional pneumoencephalography and angiography for additional study of the region are being employed with increasing frequency and are accompanied by little risk of complications. Angiography is particularly useful for determining the presence of an aneurysm or a meningioma in the region, while air studies are more useful for determining the extent of extrasellar growth of adenomas.

Surgical Technique. Having tried over the years a variety of operative approaches to the region of the sella, we have come, as a result of experience in performing hypophysectomy for cancer in over 500 patients, to adopt a similar routine in operating on pituitary adenomas.9 Other techniques serve other surgeons well and there are occasions, such as in large temporal extension of an adenoma, when the procedure needs to be varied, but any method should embody at least two highly important principles: namely, adequate exposure of the tumor and minimal retraction of the brain. The one makes for adequate removal of the tumor and protection of adjacent structures, particularly the optic nerves, the chiasma and the hypothalamus. The other reduces to a minimum subpial hemorrhage, cortical laceration and postoperative edema of the brain.

Endotracheal ether following a brief induction with Pentothal has been the anesthetic agent of choice. More recently, methoxyflurane,10 which has all the anesthetic properties of diethyl ether but is nonflammable, has replaced ether. Controlled hypotension by the use of Arfonad is established at the very start of the operation and continued till the wound is closed. This minimizes nuisance bleeding, speeds the operation and reduces somewhat the size of the brain.

The patient's head is not turned, but the head and neck are extended and the table is placed in moderate Trendelenburg position. One and sometimes two #17 spinal needles with end and side openings are introduced in the lumbar subarachnoid space and attached to 50 cc. syringes by tube. The patient then lies supine on a special mattress with an aperture for the spinal needles. A coronal scalp incision placed just behind the hairline has cosmetic as well as other advantages. The soft-tissue flap reflected over the brow includes the periosteum. The craniotomy is made on the right side, even when the left optic nerve or tract seems to be more involved, unless air studies or angiography had
shown a large temporal extension, in which case it may be appropriate to direct the exposure farther back on the side of the growth. A left-handed surgeon may prefer a left-sided craniotomy.

Four openings are made in the skull, placed without regard for the frontal sinuses. One opening is made with a 7/8 inch trephine in the midline just above the root of the nose. This will expose the sagittal venous sinus and may enter the frontal paranasal sinus. With care, the mucosa of the sinus can often be preserved; if not, the opening is plugged with a cotton pledget till time to close the wound. If the frontal sinus is very large and the bone removed by the trephine is only the anterior wall of the sinus, then a small opening just large enough to pass a saw guide is made in the posterior wall of the sinus. A second opening is made with the trephine farther up on the forehead, but offset from the midline to avoid the sagittal sinus. Two burr holes are then made in the bone just beneath the attachment of the temporal muscle and fascia, which have been divided, leaving a narrow strip of fascia attached to the bone for re-approximation of the fascia when closing the wound. The bone between the two temporal openings is partly cut through with a Devilbliss craniotome; the rest of the bone-plate is cut out with Gigli saws and a free bone plate is removed. If the frontal saw-cut passes through the frontal sinus the open sinus is plugged with cotton temporarily. It is most important not to tear the dura mater if possible.

The dura mater is then opened with a straight transverse incision about 1 cm. above the bony margin in the brow and simultaneously all spinal fluid is withdrawn. If fluid is withdrawn before this time there is less protection for the brain and subdural blood may collect if veins along the sagittal sinus should accidentally be torn while opening the skull.

In lifting the right frontal lobe from the floor of the frontal fossa it may not be necessary to hold the edge of the retractor near the midline against the falx as is required when performing a total hypophysectomy. The retractor may be angled slightly from the side, thus obviating deliberate section of the right olfactory nerve and of small veins joining the sagittal sinus. But, if this more lateral approach is found not to be propitious for good exposure of the tumor the retractor can be replaced nearer the falx.

Usually the combination of a smooth anesthetic, induced vascular hypotension and evacuation of all the cerebrospinal fluid makes it unnecessary to employ more than gentle retraction. If this is not the case, one has recourse first to the use of positive-negative pressure anesthesia to which the anesthetist can readily change, or, if this is still insufficient, intravenous urea or mannitol can be administered. We prefer not to use the dehydrating agents except when the other measures are inadequate, because of too lax a brain when it comes time to close the wound. It should be necessary to resect brain tissue only when hemorrhage occurs into it from accidental laceration or when confronted with a large extrasellar growth of the tumor.

But for exceptional circumstances, the tumor will be found to bulge from the sella, displacing the optic nerves laterally and lengthening them so that the chiasma lies behind the margin of the tumor, often concealed until the tumor is reduced in size. Any excessive manipulation of the nerves and chiasm is to be avoided; it is not even of advantage to try to protect them by a covering cotton pledget, but safer to have them always in view. A misdirected forceps or sucker tip may produce irreparable damage to the nerves and must be avoided, but this is what neurosurgery is about.

It is well to aspirate the tumor even though angiography has given assurance that an aneurysm is not present. If the tumor is cystic it is of some advantage to know the amount of fluid and whether it is xanthochromic, bloody or contains cholesterol crystals that may help to identify it as a craniopharyngioma.

The presenting part of the tumor is usually covered by the thinned-out and stretched diaphragma sellae which should be carefully
coagulated and incised. If the tumor is cystic the presenting wall, made up principally of the diaphragm, will collapse and fall away from the optic nerves and chiasma; this part of the tumor and diaphragm should be excised. Some tumors are mushy and of a consistency to pass readily into a sucker, while others are firm and even tough. These latter require more patient excision by combined use of sharp curets, semi-sharp spuds or pituitary rongeurs. The tumor may extend laterally beneath the optic nerves, displacing the carotid arteries. The instruments can be used rather freely to clean out the depths of the sella in the anterior two-thirds. What remains of the normal gland can occasionally be identified and can be expected usually to lie in the posterior part of the cavity where the gland is attached to the posteriorly displaced stalk. In any case, the excision must be continued until both nerves and the chiasma can be seen to be free of pressure from any remaining fragments of tumor. Whenever the capsule adheres excessively to the nerves or chiasma it should be left, to avoid damaging vision.

Bleeding may accompany excision of more solid tumors, but it need not be a serious problem—only a tedious one. Bleeding tends to diminish as more of the tumor is removed and temporary tamponade with a fragment of fresh muscle speeds spontaneous hemostasis better than any other method. Occasional thin muscle stamps may be left in place, but the leaving of bulky pieces of muscle or other hemostatic material is to be avoided.

One often hears reference to “prefixed chiasma” which more appropriately might be thought of as a condition in which the optic nerves are short or the tuberculum sellae is prominent, thus limiting the space in front of the chiasm through which a tumor may protrude or through which instruments may be introduced. In performing hypophysectomy on normal glands it has been found necessary to remove the tuberculum sellae for adequate exposure in about 5 per cent of cases; we have not encountered a pituitary adenoma that was wholly inaccessible from a prechiasmal approach. One may anticipate that occasion-

ally the tuberculum sellae will require resecting for improved exposure, but it must be rare indeed that there would be justification for dividing an optic nerve to gain exposure; division of the chiasma would seem more justifiable.

In closure of the wound the dura mater should be carefully re-approximated with interrupted fine silk stitches. Cerebrospinal fluid may be replaced through the spinal needle or physiologic saline may be introduced from above. If the dura mater has not been fragmented and its closure can be made water-tight, so much better. This serves two purposes: the dura mater can be ballooned out to obliterate the extradural space and also prevent leakage of fluid into the superficial tissues, thus minimizing postoperative edema of the face and scalp.

If the frontal sinus has been opened while opening the skull the temporary cotton plugs are removed and the opening is covered with a pedicle flap of periosteum held in place by a few stitches to the dura mater or by pressure of the replaced bone plate and bone button. Drains are not used except rarely a small rubber wick in the subgaleal space at the outer angle of the scalp wound.

In case the frontal sinus has been opened an antibiotic is given for a week. In such cases a superficial infection occurs in about 2 per cent and rarely ends in need for removing the bone plate.

Substitution Therapy. There is no question but that slow recovery from operation, chronic invalidism and sometimes death have been caused, particularly in years past, by hypoadrenalism which was either unrecognized or for which there was no adequate control. Many, but not all patients with pituitary adenomas, have a mild or moderate degree of latent adrenal insufficiency which becomes evident with the stress of operation. A few have more advanced and obvious deficiency before operation. Tests currently in use (particularly measurement of urinary 17-ketosteroids, 11-oxyketosteroids, serum electrolytes and the Kepler water test) provide a means of evaluating adrenal function and in turn the pituitary adrenocorticotropin
function. There is now fairly widespread practice in administering ACTH or steroids as a safety measure to all patients with pituitary tumors before and after operation. Not every patient requires treatment, but no harm comes from the practice and doubtless much good has resulted, though prolonged treatment in those who do not require it is to be avoided. Adrenal function may improve or worsen after operation, which emphasizes the equal or greater importance of testing function after operation.

Hypothyroidism is an even more common accompaniment of pituitary adenoma requiring substitution treatment.

But just as important for the surgeon is an awareness of possible alterations in electrolyte and water balance, especially in the early postoperative days. Over- or underhydration can be dangerous. The problem of recognition and management of these states is not simplified by the occurrence of diabetes insipidus, the inappropriate administration of intravenous fluids or the use of antidiuretic hormone, steroids or dehydrating fluids such as urea. Hypo- or hypernatremia of serious degree can be an accompaniment of alterations in water balance, but sometimes is apparently unrelated. The symptoms produced by these various states can easily be mistaken for those of cerebral edema or postoperative intracranial hematoma. If a degree of homeostasis in fluids and electrolytes is maintained during the acute phases, the conditions can be expected to be self-correcting.

Results of Operation. For purposes of this discussion we reviewed our operations for pituitary adenomas in the past 10 years (Table 1). There were 63 patients with chromophobe adenomas (including a few with mixed types); 5 of these patients were re-operated on for recurrence of the tumor within the 10-year period. There were 14 acromegalic patients and in 11 of these total hypophysectomy was performed. There were 3 patients with pituitary adenomas and Cushing's syndrome; in 2 of these, complete hypophysectomy was performed. This totals 85 operations performed on 80 patients, 11 of the operations being total hypophysectomy.

There was no postoperative mortality, i.e., while the patients were in the hospital. Four died from 1 to 3 years after operation, all of causes other than pituitary disease.

An account of the detailed studies of the series of cases will not be made, but a few items are of interest. The sexes were evenly divided, 39 males and 41 females. Ages ranged from 12 to 72; there were 3 patients in the 8th decade of life.

Eleven patients with chromophobe tumors and 6 with acromegaly had received adequate radiation therapy before operation, but without sufficient benefit. Of the 52 patients with chromophobe tumors not receiving preoperative radiation therapy 28 were given radiation therapy after operation and 24 were not. Two of the 5 recurrences have occurred in the 24 not receiving any radiation therapy, while the other 3 recurrences were among the 39 patients who had received radiation therapy either before or after operation. These figures are of limited value since the total number of cases is small and the postoperative time interval is short. Also, some selectivity existed in choosing to administer or withhold radiation therapy after operation. But the findings do emphasize the fact that even if radiation therapy precedes or follows subtotal removal of a chromophobe adenoma by surgery there is no guarantee against recurrence, which with our present methods of treatment can be ex-

<p>| TABLE 1 |
| Occlusion tumours |
| New York Hospital 1950-1960 |</p>
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<thead>
<tr>
<th></th>
<th>No. of Cases</th>
<th>No. of Operations</th>
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<tr>
<td>Chromophobe adenomas (including mixed types)</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Reoperation for recurrence</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Acromegalic patients (11 total hypophysectomy)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Cushing’s syndrome (2 total hypophysectomy)</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Total</td>
<td>80</td>
<td>85*</td>
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* No postoperative mortality.
pected to be in the neighborhood of 8 to 10 per cent. It is common experience that most recurrences make their appearance within 5 years.

Eleven women with chromophobe adenoma were in the premenopausal time of life and had premature cessation of menstruation. Four had return of menstruation after operation and 2 became pregnant.

Postoperative improvement in visual acuity and in fields of vision occurred in approximately 75 per cent of patients. Nearly one-third of these recovered normal vision; more than one-third had considerable improvement; the rest had some measurable degree of improvement. One patient, only, had worsening of visual acuity as a result of operation and this patient retained a degree of useful vision.

Although one of the authors (B.S.R.) performed the majority of operations, two other members of the senior staff and six of the resident staff have participated in operating on the patients of this series. All surgeons followed the same general plan of surgical technique and of postoperative care. In the entire series of patients, there was in the neighborhood of 10 per cent who had extrasellar extension of the tumor in any significant extent. These are the cases most likely to present difficulties in the operation—the cases that constitute the greatest threat to survival, but the patients cannot be treated suitably by any other method. Other surgical series report a higher incidence of these difficult cases which accounts in part for the reported mortality of the operation. Yet, the point can still be made that in this present day of improved facilities in the operating room, the efficiency of the recovery room and in the modern hospital ward where there are conveniences and understanding for post-operative care, the risk of operation on pituitary adenomas, whether partial removal of a chromophobe adenoma or total hypophysectomy in an acromegalic or a patient with Cushing’s disease, need not be formidable. When the operation is indicated, there is no substitute for it.

REFERENCES