Treatment of Pituitary Adenomas:
A study of 66 cases

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ALL TOO FREQUENTLY, the treatment of patients with pituitary adenomas is still considered in the light of the high surgical mortality and poor postoperative results of bygone years. The present study of 66 such patients demonstrates that with modern techniques, the surgical mortality is low and the results of treatment are excellent if the condition is recognised early and appropriate treatment, usually surgical removal of the tumor, postoperative radiation therapy and endocrine replacement therapy are undertaken promptly.

The successful treatment of a patient with a pituitary adenoma can be most gratifying. Restoration of vision, or maintenance of it at a useful level by the arrest of further growth of the tumor, in itself is a boon to any patient threatened with blindness. The efficacy of postoperative irradiation in controlling recurrences is well accepted, [9,10,13,15,23] and long meaningful survivals of up to 25 years [23] and 48 years [12] are not uncommon. The quality of the survival has been such that the majority of these patients can be expected to lead a relatively normal life.

Improved surgical techniques and advances in anesthesia have reduced operative mortality and morbidity, but these alone have not been enough. Of significant importance have been the recognition of pituitary deficiency states, both pre and postoperatively, and the proper use of endocrine replacement therapy prior to, during and after surgery, to enable the patient to withstand the stress of the operation and that of the postoperative period. Since the introduction of steroid substitution therapy [28], a much lower mortality and morbidity with a smoother postoperative course have been achieved. The better understanding of the responses to stress situations of a chronically hypopituitary patient has been a further step in this direction.

The radiosensitivity of the adenomas of the pituitary gland was demonstrated by the better results in those treated by surgery and X-ray when compared with those treated by surgery alone [2,3,9,10,15]. In 1936, Dyke and Hare [7], following a careful analysis, claimed a 26% success rate with only irradiation although admittedly 47.3% of their patients became worse with such treatment. Since then, with X-rays alone, success rates of 42%, [6] 50%, [26] 60%, [15] 70%, [20] have been reported. More recently, Chamlin [5] reported improvement of vision in 62.2%, maintenance of vision in 28% and that 7.9% of his patients became worse. There has thus been a tendency to over-

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emphasise the beneficial effects of radiation therapy upon pituitary adenomas while minimising the failures (those patients who got worse or did not improve) and ignoring the tragic results which can occur when a histologic diagnosis of the lesion present has not been made. Not uncommonly, one may encounter a craniopharyngioma or an aneurysm simulating a pituitary adenoma. It would be ill advised to irradiate such patients, and they may become blind in the interim of waiting for a response to the X-ray treatments. Again, the empty sella syndrome and arachnoidal cysts in and about the sella turcica can present with hypopituitary states and typical visual field defects. Irradiation again is not the answer in such cases.

In the pituitary adenoma patient, it is not possible to state preoperatively the exact extent of involvement of the visual apparatus. Irreversible visual field changes may occur while waiting for the effects of irradiation, and one may drift past the time for optimal intervention [9,10] being misled by what may appear as an apparent check in symptoms. The risk of hemorrhage into the adenoma though small is real during irradiation. Pituitary apoplexy, should it occur, can be rapidly fatal [1]. Immediate surgical intervention then becomes imperative. An emergency operation upon these patients with endocrine hypofunction is attended with much greater risk than one which can be planned and prepared for more deliberately. We, therefore, believe that those patients with impairment, either of visual fields or visual acuity, should be operated upon first and then treated with irradiation. Only patients judged to be suffering from a pituitary adenoma with no visual impairment should be treated with irradiation, without the tumors having been removed and their nature confirmed by microscopic examination. Even then, it is essential that the patient's condition be carefully followed at frequent intervals with a special concern for the development of visual impairment or evidence of hemorrhage into the tumor. The following case is a tragic example of treating what was supposed to be a pituitary adenoma by irradiation without an operation and of not following the patient closely during and after such treatment.

Case Report I.

A 17-year-old white boy was admitted to a hospital on July 16, 1961. He then had complained of severe bifrontal headaches of some 12 years' duration. His parents had also noted a failure on his part to mature both physically and sexually. For some nine years prior to his first admission, he had complained of intermittent episodes of "fuzzy vision". However, repeated ophthalmologic examination during those episodes failed to reveal any visual abnormality. There was no history of generalised weakness, unusual weight gain or weight loss. On examination, he was found to be 62 inches tall and weighed 120 pounds. He was described as being underdeveloped for his age. He showed no evidence of secondary sexual characteristics. Also, he was described as having a preponderance of fat in his gluteal and thigh areas. His skin was thickened, dry and hyperkeratotic.

A review of his systems and, in particular, a neurological examination at that time did not reveal any other abnormalities. His visual fields were recorded as being normal. There was no mention of his visual acuity. Laboratory investigations on his first admission revealed no significant abnormalities other than a low protein bound iodine (2.8 mg%), a basal metabolic rate of −17%, and low 17 − ketosteroids (2.6 mg). These, together with the Robin Kepler power water loading test, supported the diagnosis of significant adrenal insufficiency. In the latter test, none of the 4-hourly specimens or urine exceeded the overnight volume of 700 ml.

Roentgenograms showed open epiphyses appearances compatible with a bone age of 12 years, indicating a 5-year disparity from his chronologic age. X-ray examination of his skull revealed an enlarged sella turcica with deossification of the posterior clinoids. No calcification in or above the sella were to be identified.

An unjustifiable diagnosis of pituitary adenoma was thus made on the basis of his endocrine status and X-ray appearances of the sella turcica. Based on the recommendations in the literature that pituitary adenomas be treated with irradiation without surgical treatment and confirmation of the tumor, he was then given X-ray treatment. He received 6,000 rads in divided doses over a 31-day period. This was completed on 8-23-61. At no time during his X-ray treatment or after, till the time of his admission to our service on October 4, 1961 did he receive a detailed examination of his visual status.

His admission on 10-4-61 resulted following his complaint of progressive visual loss in both eyes, especially his left. Examination revealed that his visual acuity was 20/200 on the right and a paltry 1/200 on the left. Examination of his visual fields revealed large temporal field defects. Funduscopy showed optic atrophy on the left side. The fundus was normal in appearance on the right. Cerebral angiography confirmed a suprasellar mass. At operation, a cystic cra-

niopharyngioma was found and completely removed. Postoperatively, he developed transient diabetes insipidus. He otherwise made an uneventful recovery. He continues to require endocrine replacement therapy. The tragic part of it is that he is blind in his left eye. Fortunately, vision in the right eye has recovered to 20%25.

This case emphasises the need for careful selection of patients prior to advising radiotherapy on the presumptive diagnosis of a chromophobe adenoma. If a craniopharyngioma is suspected, as it should have been in this case in view of the patient's age and the long standing history of headaches and retarded growth and development, one should not temporise with X-ray treatments.

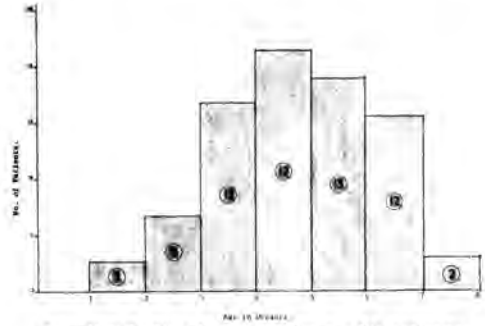
It is the purpose of this communication to report a review of our patients with pituitary adenomas during the past 27 years (1942-June 1969). In addition, we feel that insufficient emphasis has been placed by most writers on the value of steroid and endocrine therapy pre and postoperatively. Further, too many physicians are still influenced by the high operative mortality of bygone years. The long term management of the endocrine deficient patient and the problems associated with it, the management of transient diabetes insipidus and hypopituitary states require expert, careful and constant attention. This is done primarily by one of us (F.L.). Electrolyte balance and the proper understanding of the concepts of inappropriate antidiuretic hormone have also helped calm what formerly was all too often a stormy postoperative course.

The high operative mortality of earlier reports, 13.1% [10], 13.6% [6], 14.1% [16], 11.3% for chromophobe adenomas [2], 7.7% [23], 12.7% [22], 10% [8], 6.8% [27] and a quite commendable 4.9% overall mortality in the Cushing series as reported by Henderson [13] (4.5% for the transfrontal approach), compare strikingly with that of no mortality in 63 consecutive operations for the period 1951-60 in the New Hospital [24]. Our case mortality (two deaths) for the past 27 years ending June 1969, is 4.0%, with an operative mortality of 3.6%.

The present study comprises 66 patients with pituitary adenomas. Of these, 50 were operated upon. Two of these operations were in acromegalic patients without visual compromise of significance, and the rest were for chromophobe adenomas. There were five re-operations for tumor recurrences. Ten patients received X-ray treatment alone. Two patients died shortly after admission. Both were admitted comatose and in circulatory collapse, following pituitary apoplexy. On autopsy, both of them showed evidence of recent sizeable hemorrhages into their pituitary tumors with extravasation into the subarachnoid space. Both patients harboured chromophobe adenomas. Another patient was too ill with renal failure and hypertensive heart disease to withstand surgery. Two patients refused treatment after a diagnosis had been made, and one was operated upon elsewhere after the diagnosis of a pituitary tumor was documented by us.

Age and Sex

Of the 66 patients, 39 were males and 27 females; 86% of the patients were between the ages of 30 and 69, the greatest number falling between 40 and 49 years (fig. 1). Our youngest patient was 19 years old, and the oldest in this series was 75 years of age.



Age distribution histogram in our 66 patients with pituitary tumors

Fig. 1

Symptoms

Visual impairment or visual difficulties was the single most common symptom occurring in 78.8% of the patients. Visual complaints comprised any or all of the following: failing vision, failure to perceive one or both temporal fields or double vision. Not uncommonly, patients were referred by an ophthalmologist with documented visual field defects or documented progressive decrease in visual acuity. Some of these had been detected on routine eye examination. Forty-two (63.6%) of the patients had complaints of endocrine or metabolic deficiencies, e.g. amenorrhea, impotence, acromegaly, obesity, diabetes mellitus, etc. (tables I and II); 21.2% of our patients had headaches. In Rand's series [23] 19% had headaches. Two patients were admitted because they were discovered to have enlarged "ballooned out" sella turcicas when X-ray examinations of the skull were made for some other unrelated condition. One was seen following a

head injury. X-ray examination of his skull revealed an enlarged sella turcica. There were no changes in his visual acuity or visual fields. During an endocrine evaluation, he left the hospital against advice. The other patient was diagnosed as having Parkinson's disease. As was customary in all such patients, an X-ray examination of his skull was made. This also revealed an enlarged "ballooned out" sella turcica. He had no visual changes and following an endocrine evaluation received X-ray treatments.

Diagnostic Procedures

In this category, we include detailed examination of visual acuity and visual fields, X-ray examinations of the skull, cerebral angiograms, radioactive brain scans and pneumoencephalograms. The examination of visual acuity and visual fields should not be treated lightly. Outside of neuroradiologic studies, it is the most useful single examination. It localises the lesion and gives a fairly good indication of the degree of compromise of the optic pathways. Good preoperative visual fields are essential if one is to follow these patients postoperatively in any meaningful way. The examination of the visual fields and visual acuity should not be relegated to an inexperienced person.

In the present series, 46 patients had documented visual field defects preoperatively and 48 showed significant decrease in visual acuity in one or both eyes. Thirty of the 46 patients had bitemporal hemianoptic defects, but when lesser defects in the visual fields, quadrantanopsias, constriction of the temporal fields, etc., are included, 69.7% of our patients had defects in their visual fields. This compares with Cushing's 65% (Henderson), [13] and Olivecrona's 63% (Bakay) [2].

Forty-seven patients (71.2%) had unequivocal evidence of an enlarged "ballooned out" sella turcica. Erosion of the anterior wall with cavitation of the floor and erosion of one or both anterior clinoids contributed variously to the sellar enlargements. Suprasellar calcifications were present in three patients. It should be emphasised here that a normal appearing sella turcica on plain X-ray films does not exclude the presence of a pituitary adenoma, as we have seen several such.

Cerebral angiograms were performed in 43 patients. Thirty-six of these were considered positive for a suprasellar mass as evidenced by tenting and straightening of the first portion of the anterior cerebral artery, with or without associated stretching and lateral displacement of the cavernous or terminal portions of the internal carotid artery.

TABLE I

Complaints	Visual	Endocrinologic	Headaches
Number	52	42	14
Percentage	78.8%	63.6%	21.2%

Presenting complaints in 66 patients

TABLE II

Type	No.
Panhypopituitarism	31
Hypothyroidism	9
Hypoadrenalism	1
Diabetes Mellitus	1
Total —	42

Table of patients with documented endocrine deficits

Nineteen patients had radioactive brain scans. Only four were positive for suprasellar tumors which subsequently were shown to be chromophobe adenomas. The positive scans were those that showed an increased area of isotope uptake in the suprasellar area in both the anteroposterior and lateral views. The uptake in one instance was so intense as to cause us to strongly consider a suprasellar meningioma in the differential diagnosis (fig. 2.).

Plain skull X-ray examinations, with or without spot films of the sella turcica and tomography, together with radioactive brain scans and cerebral angiographic studies, were sufficient to localise structurally the lesion in all but seven of our patients, thus obviating the need for air studies routinely. However, in the preoperative evaluation of the patient, should the skull films and cerebral angiograms be negative, a pneumoencephalogram is in order. Under these circumstances, we prefer to do a fractional air study with the aid of the image intensifier. Should a tumor be present, it can be readily outlined. The procedure is short and performed with little in the way of discomfort to the patient. It is done as follows: The patient is seated with the head flexed. A lumbar puncture is performed. Five to six ml. of room air are then slowly injected. With the image intensifier and television monitoring, the air in the cisterna magna and the fourth ventricle is usually well outlined with this amount of air unless the cisterna magna is unusually capacious. Although air may have entered the third and lateral ventricles, this is usually not seen until a lateral autotomogram is exposed. This, under normal circumstances, outlines, besides the cisterna

Fig. 2

Brain scan with suprasellar pickup (AP and Lateral). Technetium 99^{m} Brain scan in a case of verified chromophobe adenoma.

magna and the fourth ventricle, the aqueduct of Sylvius, third ventricle and some of one or both lateral ventricles. The head is now hyperextended and a further five ml. of air are injected. The prepontine, interpeduncular, parasellar, chiasmatic cisterna and, rarely, the cistern of the lamina terminalis are outlined. By this method, there is a minimum of subrachnoid air laterally to interfere with the visualisation of midline structures. Should a suprasellar tumor be found, it is well delineated by the above method. The patient is then returned to his room. He is allowed up later that evening.

We performed eight pneumoencephalograms by the above method in patients having pituitary tumors. Four were positive for a suprasellar mass.

Mode of Treatment

A total of 50 patients were operated upon. There were five reoperations for recurrences (excepting the patient noted in Case Report II below, these were anywhere from three to eight years after their initial operation) and a total of five patients received X-ray therapy before an operation was thought to be indicated. Ten received X-ray therapy alone (table IV). All 55 operations in the 50 patients were performed by the transfrontal route. Of the reoperations, all were for tumor recurrence. There were no reoperations for the evacuation of blood clots or because of edema postoperatively.

TABLE III

Total Number with Documented Visual Difficulties = 52 (78.8%)		
Field defects 46 88.4%	Decreased Acuity 48 92.3%	Diplopia 6 13.5%

Types and percentage of visual abnormalities amongst 52 patients with visual complaints.

Before the radiosensitive nature of these tumors became established, not all patients received X-ray treatments postoperatively. Since that time, we have not withheld its use whenever so indicated. When it was used postoperatively, it was begun anywhere from seven to ten days after the operation. Each patient received 3,500 – 4,500 rads in divided doses over a four to six week period. Of the five patients reoperated upon for tumor recurrence, three did not receive X-ray therapy postoperatively after the first operation. One did. The other, a 48-year-old man, was initially treated with X-rays elsewhere prior to operation. He is a tragic example of treatment with X-ray alone, without a careful follow-up of the visual status. He became almost blind before being referred for an operation.

Case Report II

A 48-year-old white man saw his doctors in 1947 after two years of headaches and impotence. An X-ray examination of his skull then had shown, apparently, an enlarged sella turcica. He was then treated with X-rays but the number, duration or dosage of X-ray treatments that he received was not available to us. He certainly did not receive an examination of his visual acuity or visual fields during or following his X-ray treatments.

He was first seen by us in September 1954 with complaints of progressive visual loss in both eyes since irradiation. Examination at this time revealed that he could just perceive light in his left eye. The visual acuity on his right was 20/50. In addition, he

had a large temporal field cut on the right side. X-ray examination of his skull showed an enlarged eroded sella turcica. At operation, a chromophobe adenoma with considerable extrasellar extension was removed. In October of the same year, his visual status was unchanged on the left but the acuity on the right eye was recorded as being 20/20 and the large field defect on the right had completely disappeared. He suffered a recurrence in April 1955. At reoperation, extensive lateral spread was found under the temporal lobes. The tumor had also grown upward into the hypothalamus and third ventricle. He was last heard from in August 1955. He is presumed to have died shortly thereafter.

Operative Procedure

As indicated earlier, a transfrontal approach was employed in all our patients; 20% intravenous Osmitrol and continuous drainage of spinal fluid with a malleable needle in the lumbar subarachnoid space were employed routinely. A bifrontal skin flap was raised and the bone flap was "turned" on the side of maximal involvement of the visual apparatus, or on the right side if there was no indication to operate on the left. Through all intradural approach, the frontal lobe was elevated. Whenever the visual pathways are involved by a pituitary adenoma, the tumor will be found to have either stretched the diaphragma sella upward or to have broken through it. The optic nerves will then be seen to be stretched over the mass. In advanced cases, they may be quite flattened and atrophic. The chiasm of the optic nerves is usually hidden from view until some tumor is removed.

In all cases, an attempt at aspiration of the tumor with a fine needle is in order when it is first exposed. Varying amounts of cystic fluid may be evacuated resulting in better visualisation of the surrounding structures. In the days prior to angiography, this procedure was crucial in avoiding a fatal hemorrhage from an aneurysm in this location. Even now, cerebral angiography does not invariably disclose the presence of an aneurysm rather than a tumor, and a fine needle hole is far safer than a stab wound. If no aneurysm is found, the capsule is incised, at which time some soft grayish gelatinous tumor may extrude. The tumor is then removed with small spoons, rongeurs and suction. Because of the usual consistency of these tumors, suction is particularly useful in their removal.

After the tumor has been completely removed, the superior capsule of the tumor can often be separated from the under surface of the brain with gentle traction and blunt dissection. If it is obviously adherent, the surgeon should not persist in attempting to remove it. It is important that the optic chiasm and nerves be completely decompressed in one way or another. In the past when adequate replacement therapy was not available, it was not thought advisable to remove these tumors completely. This is no longer the case. On the other hand, removal of the capsule is not important and obviously can never be complete. If it can be partially accomplished, a complete removal of the tumor can be more readily and certainly obtained.

On completion of the tumor removal and adequate decompression of the visual apparatus, hemostasis is assured. This is followed by a careful dural closure. The dura mater is now tented to the bone edges to prevent possible epidural bleeding postoperatively. When the frontal sinus is opened, and this is to be avoided whenever possible, a periosteal flap is fashioned and sutured to the dura over the sinus. The bone flap is now anchored in place with stainless steel sutures. It is our practice to trephine a bone button in the frontal area for cosmetic reasons. This is also replaced and held by stainless steel sutures. The scalp is now closed in two layers. When the frontal sinus is opened at surgery, antibiotics are given postoperatively for ten to 14 days to prevent a bacterial meningitis.

More recently, there has been a trend towards a transphenoidal approach for the removal of pituitary adenomas. Cushing [13] employed it widely before abandoning it for the transfrontal route with a significant reduction in his operative mortality. Present day antibiotic therapy has largely offset the fear of bacterial meningitis that could follow operations transphenoidally. Further, microsurgery and the image intensifier have enhanced this procedure. We believe that a transphenoidal approach should be restricted to cases where the growth, if it be present, does not extend beyond the diaphragma sella. We further believe it has a real place in elective hypophysectomies for cancer, diabetic retinopathy and biopsy of masses arising from the clivus or its surrounds e.g. chordomas, giant cell tumors of bone, etc. We shall discuss the transphenoidal approach to pituitary tumors later.

Operative Mortality

Patients dying within 30 days of surgery were considered operative deaths. We had two deaths.

One was a 29-year-old man with a nine-year history of progressive visual loss and was almost blind.

He was operated upon in 1946. At operation, he had considerable extrasellar extension of his tumor, necessitating prolonged retraction of his frontal lobes. This was in the pre-steroid era and before the use of dehydrating agents and spinal drainage to reduce the volume of the brain during operation had become common practices. He died on the third postoperative day. Autopsy revealed cerebral edema and infarction of both his frontal lobes, and uncal herniation.

The second death occurred in a 46-year-old woman. Brisk hemorrhage from, in and around the capsule was difficult to control. Postoperatively, she was hemiparetic. Three days later she was decerebrate. She died on the sixth postoperative day. Autopsy revealed a rather large intracerebral hematoma in the temporal lobe that extended to the cerebral peduncle on the left. The two deaths gave a case mortality of 4.0% and an operative mortality of 3.6%.

Histopathology

All but two tumors microscopically verified on surgical specimens were chromophobe adenomas. The two were acidophilic tumors. Both were removed from patients suffering clinically from acromegaly.

Postoperative Course

The postoperative course is largely that of any frontal craniotomy. Transient bloody cerebrospinal rhinorrhea occurred in those where sinuses were opened at surgery. They were kept flat in bed until the rhinorrhea subsided. It usually did so within a day or two. These patients were placed on antibiotics for ten to 14 days postoperatively. We had no occasion to repair the leak surgically in any of our patients. Those patients who developed diabetes insipidus did so anywhere from 12 to 72 hours postoperatively. The management of these patients will be alluded to shortly.

The general postoperative course was otherwise a smooth one. Since 1951, patients received cortisone before, during and after surgery. When dexamethazone became available, it was used postoperatively. Of all factors responsible for a reduction of operative mortality in brain tumors, the most significant has been dexamethazone [19]. When dexamethazone was employed, it was tapered off by the 7th postoperative day. Cortisone replacement therapy was then begun. Anywhere from the 7th to the 10th postoperative day, X-ray treatments were started. Some patients received these on an outpatient basis. Following discharge from the hospital, the patients were closely followed by both the endocrinologist and the neurological surgeon. Periodic checks of the visual acuity and the visual fields were routinely made. This proved to be the most useful single examination for the detection of early tumor recurrence.

Both pre and postoperative visual fields were available for comparison in 40 patients. Of these, 33 (82.5%) showed significant improvement in their visual fields. A total of 13 (32.5%) had complete restoration of their visual fields to normal. Thirty patients (75%) had a significant improvement in their visual acuity, but only seven (17.5%) had restoration of their acuity to normal.

The postoperative fields in those treated with operation alone were compared with those who had X-ray therapy following surgery. In the former group, 72.7% showed improvement in their visual fields, while 86.2% showed this in the latter group (table V for details). It is obvious, however, that these groups are too small for these differences to be significant. Ten patients were treated by X-ray alone. Of these, four had normal vision prior to treatment. Of those with impaired vision, two were improved and one patient had restoration of his vision to normal. It should be noted, however, that this group is not comparable to those who were operated upon as only those with no visual field defect or only minor ones received X-ray therapy alone.

Patients with pre and postoperative studies of their visual fields, whose fields prior to their being seen by us were available, were divided into two categories. Those seen for the period 1942 to 1959 (group I), and those seen from 1960 to 1969 (group II). Twenty-two of the 24 patients (91.7%) in Group II had complaints of under 40 months' duration. Whereas, only six of the 15 (40%) in Group I fell in this denomination, while nine (60%) had had symptoms for more than 40 months. In Group II, 20 (83.3%) showed significant improvement in their visual fields with treatment compared to nine (60%) in Group I.

Admittedly, there are many factors that account for the differences between Groups I and II. Amongst these may be mentioned earlier referrals, improvements in anesthesia, surgery and in X-ray therapeutics. Nevertheless, it appears clear that better results are obtained from treatment, so far as impairment of vision is concerned, in patients whose symptoms have been present for shorter periods of time.

Preoperative Evaluation, Preparation and Postoperative Endocrine Management of Patients Undergoing Pituitary Surgery

Forty-two of the 66 cases in this series showed

evidence of endocrine deficiencies based on clinical and laboratory evaluation. Thirty-one cases showed evidence of pan-hypopituitarism. Nine cases demonstrated only hypothyroidism. One case demonstrated only hypoadrenalism and one case only diabetes mellitus. (table II) One instance of persistent hypercalcemia was noted in a patient with a suspected chromophobe adenoma. In no instance was diabetes insipidus present preoperatively. But in nine cases postoperatively, this complication lasted more than the usual transient four to six day period of time and in two of these instances, this complication has been prolonged (two years). One patient, with a chromophobe adenoma, postoperatively developed diabetes mellitus with hyperglycemic non-ketotic acidosis. A single instance of inappropriate ADH secretion was seen postoperatively.

The pertinent baseline studies consist of serum electrolytes, glucose, calcium, phosphorus, BUN, P.B.I. or T4 and urinary 17 ketosteroids and 17 ketogenic steroids. Cortisone acetate 50 mgm. I.M. q. eight hours is started 48 hours before surgery. On the

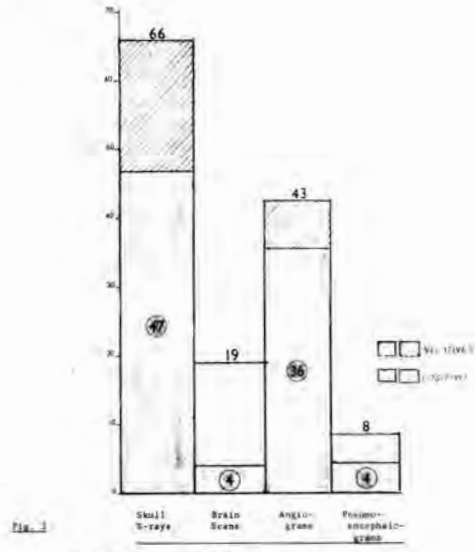


Fig. I

HISTOGRAM OF POSITIVITY OF RADIODIAGNOSTIC STUDIES

(Numbers on top of the histograms indicate the total number of each corresponding study. Those within the histograms, the number that was interpreted as being positive or negative for a tumor.)

Group I (1942-1959) = 15 Patients

Group II (1960-1969) = 24 Patients (See Text for Details)

Fig. V

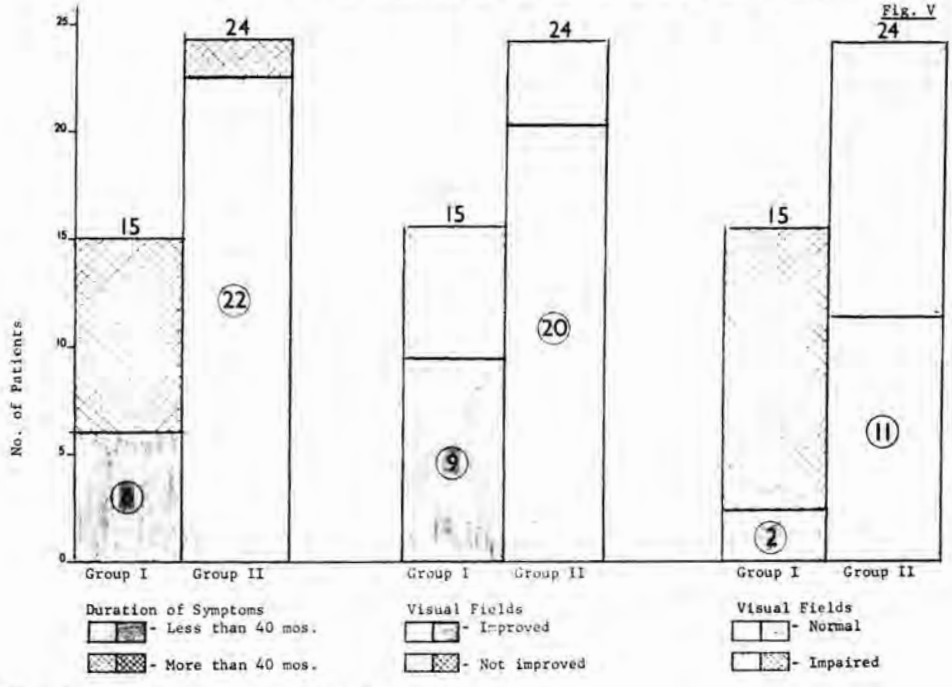


Fig. IV. A COMPARISON BETWEEN GROUPS I AND II

(See text for further details as to postoperative improvement in visual fields.)

morning of surgery, 100 mgm. cortisone acetate is given intramuscularly. Patients weighing 150 pounds or more received 200 mgm. of cortisone intramuscularly instead. At the onset of surgery, an infusion, consisting of 100 mgm. Solu-Cortef dissolved in 500 ml. of 5% glucose, is administered over an 8-hour period. Patients who did not receive dexamethazone postoperatively were given 50 mgm. of cortisone acetate every eight hours for two days. This dose was then reduced in a stepwise fashion so that by the 8th postoperative day, the patient was on this maintenance therapy. This consisted of 25 mgm. of cortisone acetate each a.m. and 12.5 mgm. each p.m. Those receiving dexamethazone postoperatively were not started on the above maintenance therapy till after the dexamethazone was tapered off. This usually took about five days. This course of supportive steroid therapy has eliminated any signs or symptoms of adrenal insufficiency and has allowed the postoperative recovery phase to be smooth and afebrile. This regime of adrenal steroids does not seem to enhance the appearance of diabetes insipidus postoperatively.

TABLE IV

Type	No.
1. No. treated by surgery, X-ray or both	60
2. Pituitary apoplexy	2
3. Refused treatment	2
4. Treated elsewhere Operated by Dr. W. Hamby	1
5. Too ill for treatment	1
Total	66

Methods of treatment of 66 pituitary adenoma patients.

Diabetes insipidus occurs transiently in the majority of the cases postoperatively. It usually occurs 12 to 72 hours postoperatively and is thought to occur when no other cause for diuresis is apparent (urevert, excessive I.V. fluids). It is judged to be present when the urinary output exceeds 200 cc. per hour and/or when the specific gravity of the urine is below 1,005. Transient diabetes insipidus of less than 48 hours' duration is treated with aqueous Pitressin 0.5 to 1.0 units I.M. every six to eight hours. Diabetes insipidus for more than 48 hours is treated with Pitressin Tannate in oil (five units) 1.0 ml. I.M. every 24 to 72 hours. If continued use of Pitressin is indicated, one can switch to the nasal insufflation of powdered posterior lobe extract every four to six hours. Most patients in this series who developed diabetes insipidus postoperatively had this condition for only two to four days, a few for one week and only two patients in the entire series required long term (two years) control of diabetes insipidus. These two patients did not respond to Chlorothiazide therapy.

Although secondary hypothyroidism was a frequent preoperative finding, it was never severe enough to postpone surgery, except in one instance. Thyroid replacement is started one week after surgery with 30 mg. thyroid extract or 0.05 mgm. synthroid daily and gradually increased over a period of several months to full replacement dosages.

Androgen replacement therapy consisting of 15 to 20 mgm. of methyl testosterone sublingually or in the buccal pouch was used in those males complaining of weakness, loss of libido and potency. Estrogen replacement was routinely used in premenopausal females and in post-menopausal females demonstrating osteoporosis.

Discussion

In performing neuroradiologic studies, one should avoid redundant tests. We have found little use for air studies in view of the information derived from the history, clinical examination, visual field examinations, X-ray examination of the skull, radioactive brain scans and cerebral angiograms. However, in the event of these studies being inconclusive, an air study is in order. We performed only eight pneumoencephalograms in this series. Lewtas [21] makes no mention of cerebral angiography in his discussion of radiology in the diagnosis and management of pituitary tumors. He relies on X-ray examination of the skull and air encephalography. We have found cerebral angiography to be particularly useful in excluding aneurysms about the sella turcica and other suprasellar tumors. A tuberculum sella meningioma was thus diagnosed in one of our patients with signs and symptoms not unlike those of a pituitary tumor. Poppen [22] has used cerebral angiography to determine if the optic chiasm is pre or post-fixed relative to the sella turcica. We do not employ cerebral angiography for this purpose, nor feel that it is reliable in this regard.

The need for histologic verification of the lesion with which one is dealing cannot be overemphasised. Our Case I noted earlier would attest to this. However, operation we feel is less warranted in those with evidence of a pituitary adenoma without any visual compromise. The exception to this is the patient with early onset of gigantism or acromegaly.

Recently, opinion has been expressed by Ray [25] that chromophile pituitary adenomas associated with

acromegaly should be extirpated surgically. This position is justified and one which we have come to accept, especially in those patients suffering from acromegaly or gigantism where the somatic effects are not far advanced. In these cases, the primary concern is with the disfigurement of the patient and seldom with vision. It is now established that in early cases of acromegaly, the disfigurement can be arrested or even made to regress in many instances if the offending tumor is promptly and completely removed. These patients are entitled to this possible relief and should not be subjected to less effective radiation therapy merely because their vision is neither involved nor threatened. It is probable that many acromegalics without visual impairment are best operated upon by the transphenoidal approach.

The high operative mortality of early reports were no doubt due in some measure to larger tumors and the unavailability of steroids. Today patients are being seen earlier. This and endocrine therapy, better anesthesia, improved surgical techniques and postoperative care have all been consonant with the reduction in operative mortality and morbidity.

All our operations were performed by the transfrontal approach. We report an operative mortality of 3.6%. Recent reports in the literature [4,11,12] attest to the low mortality and morbidity following a transphenoidal approach to these tumors. Hamlin [11] reported a mortality rate of less than 2% in 104 patients undergoing transphenoidal pituitary tumor excision and Hardy [12] had none to report in a series of 20 consecutive operations for pituitary adenomas. Guiot (personal communication) has extended this procedure to remove craniopharyngiomas, but this he does not do unreservedly. We believe that a transphenoidal approach should be restricted to cases where the growth does not extend beyond the diaphragma sella. We further believe it has a real place in routine hypophysectomies, acromegalic patients without visual field defects, and in small pituitary adenomas. We have employed it in hypophysectomies for diabetic retinopathy, metastatic breast cancer and for the biopsy of sphenoidal masses. Any evaluation of the transphenoidal approach must take into account the known occurrence postoperatively of cerebrospinal fluid rhinorrhea in some cases and the obviously greater risk of intracranial infection with the transphenoidal approach as compared with the transfrontal.

We fail to see, however, how by a transphenoidal route adequate decompression of the optic nerves and chiasm can be assured, especially in those cases where a "meaty" tumor is located above or on these structures. We are agreed that with proper selection of patients, the transphenoidal route may be employed for tumors that are wholly intrasellar. However, except for the patients with acromegaly, there is little indication for recommending surgery for wholly intrasellar pituitary tumors. When suprasellar extension is present a transfrontal approach is best suited for decompression of the visual pathways under direct vision.

Most of the patients undergoing transphenoidal surgery are also being given radiotherapy. As a result, it is difficult to assess the efficacy of this form of treatment. In the cases reported by Hardy [12] 13 of his 16 pituitary adenoma patients had field defects. He does not state what these field defects were. Following operation and X-ray therapy all but three had what he categorises as "complete improvement". But of the cases with "complete improvement", all but one had symptoms of less than ten months' duration. Further, eight in this group had had symptoms for less than six months. It is this category of patient which is often helped by irradiation. Further, it is somewhat early to study these patients from the point of view of recurrence. Most reports in the literature (and our own experience would concur) indicate that should a recurrence occur, it is most likely to appear between the third and the fifth years following treatment.

That X-ray therapy has a definite and important role in the treatment of the pituitary adenoma patient is not disputed. Our best results have been in patients who were treated with X-rays following surgery. Further X-ray therapy reduces the likelihood of a recurrence. Three of our five patients, who had a recurrence, had not received X-ray therapy following surgery.

Svien et al [27] recently reported on a comparison of visual changes in 71 cases of chromphobe tumors before and after surgery, with 74 cases before and after treatment by irradiation alone. They came to the conclusion that radiation therapy is almost as effective as surgical removal in so far as visual changes were concerned. They utilised the American Medical Association recommendation by the Committee on Medical Rating of Physical Impairment, to quantitate visual loss. In their three categories, Stages I, II, III, they had comparable numbers of patients treated by both methods. It is apparent from Table V of their article, that 14 patients (19.7%) had their vision restored to normal after surgery compared to 9 (12.2%) in the irradiated group. This becomes more significant

when it is realised that 34 of the irradiated group had Stage I visual loss, while only 27 had Stage I visual loss in the surgical group. Further, a larger number, 23, in the surgically treated had Stage II visual loss compared to 19 in this stage in the irradiated group. Moreover, 36 patients (50.6%) had visual improvement of 33% or more with surgery, while 30 (40.5%) did so in the irradiated group. If this be extended to those with visual improvement of 67% or more, 23 (31%) did so following surgery, while 18 (24.3%) were able to accomplish this with X-ray.

TABLE V

Type of Treatment	Improved	Unchanged	Worse	Total
Surgery and X-ray X-ray and Surgery	25(10N)	2	2	29
Surgery alone	8(3N)	2	1	11
X-ray alone	3(1N)	4	—	7
Total	36(14N)	8	3	47

N = Normal fields

Post-treatment visual fields (where available) in those treated by the methods indicated.

Surgery would thus seem to have an edge over X-ray therapy alone. There is no doubt from the experience of others [8,10,22] and as in our own series, that those treated by surgery and X-ray had the best results; 86.2% of our patients had significant improvement in their visual fields while 40% had restoration of their vision to normal with this form of treatment. These facts justify the surgical treatment of these tumors as compared with radiation therapy alone. Further, the importance of a histologic diagnosis has already been discussed and this would obtain only in those treated by surgery.

We have indicated that visual fields should be mapped pre and postoperatively and used as a baseline for future management. They are a sensitive index of improvement or deterioration and are most helpful in pointing to a possible recurrence of tumor.

Lewtas [21] is of the opinion that postoperative fields are misleading and not reliable indices of recurrent tumor growth. He recommends approximately annual serial radiographs of the skull to enable him to examine the bony outlines of the sella turcica. However, tumor gorwth, particularly in the suprasellar region where it is most important so far as vision is concerned, is not necessarily associated with bony change and such changes, even if they occur, may lag far behind changes in vision. Further, the judgement of bone density is too subjective and given to technical variables like rotation, projection and quality of the films to make such radiological studies reliable for this purpose. We feel that the examination of the visual acuity and visual fields constitutes a most sensitive, reliable, reproducible index of recurrence. Confirmation and extent of the recurrence can then be studied by other ancillary diagnostic methods.

Summary

1. A total of 66 patients with pituitary adenomas seen and treated from 1942 to June 1969 are reviewed.
2. Progressive visual compromise has been the major criterion for surgery. It was the presenting complaint in 78.8% of our patients.
3. The pre and postoperative roles of steroids and other endocrine therapy have been emphasised.
4. Of those treated by our three methods, surgery alone, X-ray alone and surgery followed by X-ray therapy, 74.5% showed significant improvement in their visual status and of these, 29.8% had complete restoration of their visual fields to normal. The group treated by surgery and irradiation gave the best results (86.2%), had significantly improved vision and 40.0% had restoration of their visual fields to normal.
5. Our operative mortality of 3.6% (a case mortality of 4.0%) compares favourably with those of other series in the literature.

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