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SOME PROBLEMS IN THE TREATMENT OF PITUITARY ADENOMAS.

Leo M. Davidoff, M.D. *

The classical clinical picture presented by a patient with a chromophobe adenoma of the anterior lobe of the pituitary gland is well known to all of us. It presents a combination of diminished glandular function of the anterior lobe of the pituitary, and compression of the optic chiasm. It is the disturbance in vision resulting from the latter which usually brings the patient to seek medical help. This is manifested by bitemporal visual field defects which interfere with the patient's performance of his daily activities. The disturbances in endocrine function are more subtle, and may not be recognized by the patient as manifestations of the disease until this is pointed out by the medical consultant to whom he applies for relief of his visual disturbances. For to the patient himself, the changes in his physiological and constitutional status may be ascribed to variations of the normal changes that occur in a person as he matures and grows older.

These changes classically consist of drowsiness and sluggishness during working hours, and increase of weight. The skin becomes thin, soft, and pale, with a slightly yellowish tinge. The hair on the head becomes silky and thin. Pubic and axillary hair diminish or disappear. In the male patient, body hair disappears, and the beard become very sparse or stops growing altogether. He loses his libido, and his testes usually become softened. The female patient becomes amenorrheic and sterile, and also loses her libido. The blood pressure is usually lowered; fasting blood sugar may be lowered glucose tolerance is increased; basal metabolic rate is lowered; protein bound iodine of the blood, and the uptake of radio-iodine by the thyroid are diminished. Diminution in ACTH excretion of the pituitary results in weakness, lowered resistance to infection, and difficulty in coping with stress. Urinary excretion of 17-ketosteroids and corticosteroids is low, and plasma corticoids are low. In a word, the patient presents a

* Professor and Chairman, Department of Neurosurgery; Albeot Einstein, Medical School, New York.

picture of diminished gonadal, thyroid, and adrenal function, secondary to loss of stimulation of these glands by the anterior lobe of the hypophysis.

It is theoretically conceivable, since the picture just presented is one of compression of the anterior lobe of the pituitary and of the chiasma by a tumor in neighborhood of these structures, tumors other than those originating from the chromophobe cells of the anterior lobe itself may produce the same picture. This, indeed, may be the case, and in the differential diagnosis craniopharyngioma, tuberculum sellae meningioma, aneurysm of the internal carotid artery, and some of the rarer conditions such as chordoma, cholesteatoma, metastatic carcinoma, must be considered and ruled out. However, the details of this differentiation do not immediately concern us here.

The classical roentgenologic picture of our hypothetical case shows an otherwise normal skull in which the sella turcica is markedly enlarged, the floor of the sella is depressed, the dorsum sellae and posterior clinoids are elongated and thinned, and the entire enlarged sellar area shows considerable demineralization as compared to the rest of the skull.

Neurologically our patient is completely negative, except for the presence of primary optic atrophy which may vary in degree depending upon the period of time during which the tumor was of sufficient size to compress the optic chiasm, and the resulting bitemporal visual field defects.

The picture of acromegaly associated with eosinophilic adenoma of the anterior lobe of the pituitary is so striking and so familiar that we need not take time here to describe it.

The relation of Cushing's Syndrome to basophilic adenoma of the anterior lobe of the pituitary gland is still controversial, and will not come into our discussion at all on this occasion.

While diagnosis presents many a problem in the atypical examples of pituitary tumors, the clinical picture of a classical case of pituitary adenoma is, as just stated, clearly recognizable. However, the manner of treatment of these patients is still a matter of considerable controversy. The two major methods of treatment are: (1) Surgery; and (2) Radiation Therapy. In either case, of course, treatment to the tumor is supported by substitution hormonal therapy. I think it is fair to say that there are no longer any "purists" in relation to the form of therapy to be used — that is to say, there are no longer people who would treat these adenomas exclusively by surgery without ever making use of radiation therapy, nor are there any who would feel that all therapeutic efforts have been exhausted

after only radiation therapy has been applied. However, here definitely are people who prefer first to operate upon these patients, while there are others who prefer to apply radiation therapy as a primary resort, yet both groups are prepared to use both forms of therapy as they personally see the indications. Thus there are those who operate first, and apply radiation therapy in the early post-operative course routinely. There are others who operate first, and use radiation therapy post-operatively, at a later date, only if recurrence of symptoms takes place. Still others will operate **initially** only upon those patients who are in urgent need of quick relief. Such patients are those who are on the verge of blindness at the time when first seen, so that there is no time for the slower effects of radiation therapy to take place. Those cases in which the differential diagnosis is not clear, and the clinical picture could be due to some tumor other than a pituitary adenoma in the region of the chiasm, are also operated upon initially even by surgeons dedicated to a plan of initial trial by radiation. In all other instances they would prefer to apply radiation therapy first, and resort to surgery only if or when this form of therapy had failed. For brevity's sake, and following the modern fashion of identifying people, institutions, and trends by initials, we may divide these groups into the SF's (Surgery First) and the RF's (Radiation First). This is not unlike the great controversy existing in Great Britain which splits the population down the middle into the MIF's (Milk In First) and the TIF's (Tea In First) when they pour their favourite breakfast beverage. The SF's have a long tradition, which began at a time when radiation therapy was still quite primitive, and by the time more effective radiation became available they were too long accustomed to the surgical approach to change their ways. The RF's have a somewhat shorter history, and are represented, for the most part, by individuals who are primarily radiotherapists and are not, of course, themselves able to operate upon these patients. Now if it happens that a neurological surgeon become an RF, he is not so much accused of being a traitor to his profession, but rather it is said that he is a bumbling surgeon who lacks the skill to operate successfully.

If it is contended that the many advances in anesthesia and in surgical technique make the operative approach to these tumors simpler and safer even in the hands of less skilled operators, it may be cited in a parallel way that the sources of radiation, as well as the accuracy and skill of its application, have also improved enormously over that existing in this form of therapy forty years ago.

Since there has been a great deal of improvement in both the surgical and the radiological forms of therapy in adenomas of the pituitary,

it may be worthwhile, before considering the results of these forms of treatment individually or in combination, to discuss briefly the changes that have taken place in each.

As far as surgery goes, it had been established up to the time of the middle 1920's, to approach these lesions primarily through the nose, trans-sphenoidally, and into the sella turcica by way of its floor. This afforded a limited exposure of the lesion, inability to see and protect the optic nerves and chiasm, inaccessibility of the intracranial extension of these tumors, inability to deal with chiasmal tumors other than those which originated from the pituitary gland, and danger of infection from the nose.

With the increase of experience with intracranial surgery, the intracranial transfrontal approach to the pituitary region gradually and almost completely replaced the trans-sphenoidal operation from the mid-twenties onward. At first there was a somewhat higher mortality with this approach. However, as anesthesia improved, and surgical techniques were introduced including controlled hypotension, the use of steroids and diminution of intracranial pressure by hypertonic solutions such as hypertonic Mannitol or urea, continuous spinal drainage, and hyperventilation, as well as with the experience acquired by the approach to this region for total hypophysectomy in cases of breast carcinoma, the mortality and morbidity from the transfrontal operation were gratifyingly reduced. Thus Ray and Patterson (13) in a recent review of their experiences with the transfrontal operation for pituitary tumors, were able to present a series of 85 consecutive cases at the New York Hospital from 1950 to 1960 without a single post-operative mortality. Indeed, Ray's enthusiasm has led him to advocate total surgical removal of the tumor plus the pituitary gland, in such cases of acromegaly in which the sella was not enlarged or was only slightly enlarged. This condemnation of patients to a life-long dependency upon artificial endocrine replacement, however, while perhaps justifiable in breast carcinoma cases with a short life expectancy, seems to me a tremendous burden to place upon patients with a greater longevity.

At the same time that improvement took place in surgical technique in the treatment of these patients, radiation therapy also improved remarkably. The first cases were treated with an x-ray machine having a capacity of 80 to 100 kv. Gradually 250 kv. machines were made available, and from there on the kilovoltage increased up to one or two million volts. At the same time radio-isotope sources of radiation in the form of Co60, cesium, and betatron particles accelerated at 22,000,000 to 24,000,000 volts, as well as cyclotrons delivering deuteron or proton parti-

cles, have become available, so that the power and flexibility of radiation easily paralleled the improvements in surgical techniques.

While it is gratifying to see the surgical operative mortality diminishing to a negligible percent, it must also be kept in mind that the mortality from radiation therapy is largely nonexistent. The more important question, therefore, is which of these forms of therapy results in a greater percentage of improvement in patients with pituitary adenoma. Unfortunately this question is simpler to ask than to answer. For this there are a number of reasons. First, there is another alternative, namely to use both surgery and radiation in each case. However, this too is fraught with a number of alternatives. Shall one, for example, start with radiation in all cases, and follow each one with immediate post-radiation surgery? Or, shall one operate first and follow the operation by immediate radiation? Shall one, perhaps, use radiation both before and after surgery? Finally, shall one use one or the other form of treatment exclusively, and apply the other form only if the first form has failed?

The answer to these questions cannot be obtained by setting up a series of experiments, with appropriate controls, in laboratory animals. On the other hand, no one clinic has a large enough material, nor is it under the supervision of any one director for a long enough time to be able to treat enough patients with adenomas of the pituitary where the factors of histologic type, age, sex, duration of symptoms, and degree of involvement of the hypophysis on the one hand and the optic chiasm on the other, are all reasonably alike. Indeed, even if there were, a prospective study would have to divide these cases into carefully planned groups, each treated by radiation, or by surgery, or by the various combinations of these.

Anyone's individual experience, therefore, no matter how extensive, must of necessity still be inadequate to answer these questions with scientific accuracy. The best one can do is to try and bring his own impressions in line with the published results of others, and allowing for individual prejudices and temporal as well as geographic variations, draw tentative conclusions that are, as far as humanly possible, honest and unbiased.

While many reports exist detailing the results treatment alone, of the pituitary adenomas, none of these can compare for depth, extent, size, and accuracy, with the results described in the series of cases belonging to Harvey Cushing. Of the many papers emanating from his clinic, the last one by W. R. Henderson (8) in 1939, about seven years after Dr. Cushing's retirement from active surgery, reports upon the whole of

Cushing's pituitary series with a meaningful period of follow-up. There were 338 cases in that series, of which 19 died and 316 were available for follow-up. In those patients operated upon through the trans-sphenoidal route, there were symptoms of recurrence of tumor within five years after the initial operation in 67.2 percent of cases. In the patients operated upon through the transfrontal route, there were 42.5 percent of recurrences in the same period of time, thus showing the value of the more radical removal of tumor tissue.

In about the middle 1920's the late Dr. Merrill Sosman persuaded Dr. Cushing to permit him to treat the patients who were operated upon for pituitary adenomas *post-operatively* by radiation. (Practically none of Dr. Cushing's cases received radiation therapy *pre-operatively*.) The patients thus treated, namely by a combination of surgery first plus post-operative radiation therapy, showed a recurrence of tumor symptoms in only 34.7 percent of cases in which the operation had been done through the trans-sphenoidal route, compared to 67.2 percent recurrence without post-operative radiation; and of those cases in which the operation was done transfrontally, only 12.9 percent showed recurrence of symptoms as against 42.5 percent recurrence without post-operative radiation. This significant improvement of results was achieved by relatively primitive sources of radiation.

In 1948, Davidoff and Feiring (4) reported upon 51 cases in which operation was done either following or followed by radiation therapy. Recurrence of tumor symptoms occurred in nine patients, or 17.6 percent of cases.

In 1951, out of the large material from the Lahey Clinic, Horrax (9) was able to report upon 105 cases of chromophobe pituitary adenoma who had been operated upon between 1932 and 1949, chiefly by the transfrontal route, with or without associated radiation therapy. There was an over-all mortality rate of 13.3 percent, but he pointed out that 76 cases were simple tumors without intracranial extension, among whom there was a mortality of only 3.9 percent; whereas in the 29 cases of large tumors with intracranial extension, the operative mortality was 37.9 percent. Indeed, this experience has been duplicated in the clinics of Olivecrona (reported by Bakay⁽¹⁾), Jefferson⁽¹²⁾, Grant⁽⁷⁾, and Davidoff and Feiring⁽⁴⁾.

Horrax was a somewhat late convert to the extensive use of radiation therapy until the high voltage sources were available. In 1955⁽¹⁰⁾ and in 1958⁽¹¹⁾ he stressed the change in the results of treatment by irradiation when this occurred. In the period between 1932 and 1949, 89

cases were treated with conventional radiation then available, and 62.9 percent required operation anyway. Beginning in 1950, a 2,000,000 volt source of x-ray radiation was used to deliver a total dose of 4,000r to the tumor. Between 1950 and 1955, 66 cases were treated in this way, and only 12 percent of them required postradiation surgery.

Recently Correa and Lamps (3) presented their experience in 94 cases of pituitary adenoma treated with different doses of radiation. They found that:

44.4 percent showed improvement with doses of 2,000 r to 2,500 r.

60.6 percent showed improvement with doses of 2,900 r to 3,500 r

79.3 percent showed improvement with doses of 4,000 r or more.

There thus appears to be a crystallization of our experiences with radiation, strongly favoring initial trial by radiation therapy whenever possible. While statistical evidence is sometimes unconvincing if the number of cases is limited, or the results are too close to chance variations, a single striking case can prove beyond a shadow of a doubt that, in that case at least, a particular form of therapy is most effective. Once this is accepted, the logic of expecting similar results in similar cases with the use of the same form of therapy is proven. Such a case, previously reported in detail (5) is the patient whose pneumoencephalograms were shown before, and two years after radiation treatment alone.

With the use of larger doses of radiation, however, a disturbing element has crept into the picture, which may or may not be significant but needs to be reported. In 1959, Terry, Hyams, and Davidoff (14) reported upon three cases, each showing a combined non-metastasizing fibrosarcoma and chromophobe adenoma of the pituitary. One of these patients had previously been described by Feiring, Davidoff, and Zimmerman (6) All three patients showed a rapid recurrence of their symptoms after radiation, as well as after surgical therapy. The recurrences led to the use of repeated courses of irradiation, with consequently higher total doses than usually employed. The first patient had five courses of treatment during six and one-half years, with a total of 13,150 r. measured in air, or about 7,500 r. to the tumor. The second patient had three courses of therapy over thirty-four months, with a total tumor dose of about the same amount as the first patient. The third patient received about 6,500 r. This therapy was given within a period of approximately seven years. Since only one case with a similar histologic picture appears in the literature (15) and that in a patient who had never been treated with radiation, and since of the hundreds of cases of pituitary adenomas treated with radiation only these three have been reported, the relation between this malignant

degeneration and the treatment by radiation cannot definitely be established, and if a causal relationship does exist it must indeed be a rare event. It is nevertheless a reminder that inherent dangers may always be present when powerful agents like supervoltage radiation are employed.

In the decade between 1948 and 1958 the author has had under his care 108 patients with pituitary adenomas, who were divided as follows:

DOCTOR LEO DAVIDOFF'S SERIES (1948 - 1958).

Type of Tumor:	Operated:	Not Operated:
CHROMOPHOBE ADENOMAS (87)	27	60
ACIDOPHILIC ADENOMAS (21)	4	17
SERIES TOTALS: (108)	31	77

A detailed discussion of these cases will form the subject of another stantiated, namely that;

1. Operative mortality can be kept to a minimum if operation is reported. In summary, however, the experience of others already cited is subdone primarily on all cases, thus including a high percentage of small tumors without intracranial extension. However, these cases are also the ones that do best with radiation therapy.

2. Even in cases in which operation has been undertaken primarily, post-operative radiation should be used in order to diminish the danger of recurrence of symptoms.

3. Radiation should be tried first in all cases except those in which vision is threatened, or neurologic evidence of intracranial extension exists, and the delayed response characteristically seen after irradiation, is too slow to be relied upon.

4. In all cases in which radiation is used, the patient should be under most careful surveillance by a team consisting of a neurologic surgeon, a neuro-ophthalmologist, a radiotherapist, and a neuro-endocrinologist. The neurosurgeon should be the captain of the team, and must be prepared to interrupt radiation treatment and undertake surgical intervention if the patient's condition deteriorates under therapy. The neuro-ophthalmologist should study the patient's visual fields in detail at least twice weekly during the early periods of treatment, and daily or even more often during critical periods. The radiotherapist should start the treatment with small daily doses, to test patient's tolerance to radiation, after which

multiple portals should be used in daily rotation, and a total dose of 4,000 r. to the tumor should be aimed at.

5. While immediate improvement in the patient's symptoms, especially in his visual fields, is very gratifying, one should not be discouraged by a simple arrest in the deterioration of the patient's visual fields, particularly if the arrest is at a level of still useful vision. Improvement often follows months after radiation therapy is completed, and may continue for even up to four years (2).

6. In view of the possible danger of excessive radiation, it may be the part of wisdom to make use of only one series of treatments consisting of 4,000 r. to the tumor. If recurrence of symptoms should nevertheless arise, operation should be done without further irradiation.

Résumé

Une discussion détaillée fera l'objet d'un autre rapport. En resume, en tenant compte de l'expérience d'auteurs déjà cités, nous pouvons retenir les éléments suivants:

- 1 - La mortalité opératoire, peut se situer très basse, si l'intervention est effectuée dans tous les cas. Ceci comprend, évidemment, même les petites tumeurs sans extension intracrânienne; mais ce sont des cas qui répondent le mieux à la radiothérapie.
- 2 - Même dans les cas, où, l'intervention a été effectuée, elle doit être suivie de la radiothérapie pour diminuer le risque d'une récurrence.
- 3 - La radiothérapie devrait être essayée en premier dans tous les cas, excepté si la vision est en danger, ou s'il y a des signes neurologiques d'expansion intracrânienne.

La réponse tardive, caractéristique de la radiothérapie dans ces cas, est trop lente pour pouvoir compter dessus.

- 4 - Dans tous les cas où la radiothérapie est employée, le malade devrait être placé sous le contrôle vigilant d'un groupe constitué par un Neurochirurgien, un Neuro-ophthalmologue, et un radiothérapeute. Le Neurochirurgien doit être le capitaine du groupe et doit interrompre la radiothérapie, et recourir à une intervention si la condition de malade se détériore pendant la radiothérapie. Le Neuro-ophthalmologue, devrait surveiller le champ visuel du malade, au moins deux fois par semaine au début, et tous les jours et même plus pendant la période critique.

Le radiothérapeute devrait tâter la sensibilité et la réaction du malade, par les petites doses au début. Après cette période d'essai, un total de 4000 r tumeur doit être administré par différentes portes d'entrées avec rotation quotidienne.

- 5 - Tandis qu'une amélioration du champs visuel est très souhaité au début, son absence ne devrait pas être décourageant, surtout si le C.V. est dans la limite d'utile.

L'amélioration, peut se voir, des mois après la fin de la radiothérapie, et peut continuer même jusqu'à 4 ans.

- 6 - Pour éviter les dangers de la radiation, il est sage de recourir à 4000r tumeur. En cas de signes de récurrences, il est recommandé de recourir à une intervention chirurgicale sans plus faire de la radiothérapie.

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REVIEW OF 50 CASES OF PITUITARY ADENOMA
TREATED BY SURGERY.

A. Eslamdoost and N. O. Ameli *

This is a brief review of 50 consecutive cases of pituitary tumours submitted to operative treatment in the last 10 years. All these patients were operated by one surgeon (N.O.A.). Suprasellar cysts, suprasellar meningiomas and epidermoid cysts are not included. Only those patients with definite and marked visual field disturbance were accepted for surgery. The others were treated by radiotherapy alone. Unfortunately many of the patients on admission had severe visual deficit, often blind in one eye and little vision in the other.

There were 23 males and 27 females in the series. Their ages varied from 15 to 58 years. There were only three cases older than 50. In this series there were only five cases with eosinophil tumours. The rest were chromophobe adenomas. There were 3 cases with huge extrasellar extension one in the left anterior fossa, and two in the middle fossa. The case with the anterior fossa extension will be briefly described as he had some unusual features.

A conscript soldier aged 21. with obvious gigantism was admitted for investigation of epileptiform attacks. A month before admission whilst swimming had a fit which nearly caused his death. Since then he had 3 more major attacks. Vision left eye was down to hand movements. Right eye vision was normal with no field defect.

Fundi showed papilloedema on the right and optic atrophy in left (Foster-Kennedy Syndrome).

X-ray of skull showed a large sella turcica. E.E.G. demonstrated a left frontal focus. Left carotid angiogram showed a large mass in the left anterior fossa.

* Department of Neurosurgery, Phalavi Hospital, Tehran, Iran.