Pituitary Adenoma: Results of Combined Surgical and Radiotherapeutic Treatment of 260 Patients

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Several variants of surgical and radiotherapeutic technique have been employed in the treatment of pituitary adenoma, and this is reflected by the number of reports that have appeared. The earliest surgical approach was by the intracranial route (Horsley, 1906a, 1906b), which remains in use today, though the endonasal route was popular for a time (Cushing, 1912) and is still employed by some surgeons for ablation of the normal pituitary gland. Treatment of a series of patients by radiotherapy was first reported by Heinismann and Czerny (1926) ; subsequently, primary treatment by radiotherapy became customary only for tumours that did not interfere with vision, while postoperative irradiation was employed to reduce the incidence of recurrent tumour (Henderson, 1939). Despite the difference between patients treated surgically and those receiving radiotherapy, particularly in the size of tumour and in the criteria adopted for diagnosis, most studies have reported both groups of patients together. For example, Henderson's (1939) report of 338 patients treated by Cushing includes patients operated on through both endonasal and intracranial routes, not all of whom received irradiation ; while another large study, that of Bakay (1950), comprises 292 patients similarly operated on by different methods and also given radiotherapy either before or after operation. Variations in treatment also occur in the studies of Horrax *et al.* (1952, 1955), Nurnberger and Korey (1953), Mogensen (1957), Ray and Patterson (1962), and Poppen (1963). By contrast, the 260 patients in the present series were treated by the same surgical technique, and, with few exceptions, by subsequent radiotherapy.

Material and Method

The case records of the 260 patients were examined. Each patient had been operated on by one surgeon either at the National Hospital, Queen Square, or at Atkinson Morley's Hospital, Wimbledon, from 1938 to 1962 inclusive. The diagnosis of pituitary adenoma had been confirmed by histological examination in 246 patients ; in the remainder the clinical and operative findings had been characteristic.

Of the total, 145 patients (56%) were males ; the ages ranged from 14 to 72 years, the maximum incidence for both sexes being in the fifth decade. Chromophobe adenomas comprised 76%, eosinophil tumours 7%, and in 11% the adenoma contained both chromophobe and eosinophil cells. In 6% the histology of the tumour was uncertain.

In addition to the normal details of operative findings and progress, each case record included a series of replies to an annual request from the surgeon for information about the patient's health. Although these letters rarely gave medical information, the patient's progress was recorded, and as relatives became aware of the hospital's continued interest deaths were also reported. Since operation 88 of the patients had died and contact had been maintained with all but nine of the remainder. A request for their co-operation in this investigation was sent to the remaining 163 patients ; consent to examination was ultimately obtained from all but one. Ten patients resident overseas were questioned by letter ; the remaining 152 accessible patients were all examined personally, either in hospital or at home. Details of the patients' preoperative symptoms and signs, the operative findings, the results of investigations, the symptoms and signs, including visual acuity and fields at the time of examination, the results of investigation, and information about replacement therapy were entered on prepared forms and on punched cards.

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Surgical and Radiotherapeutic Treatment

The indications for operation, and the surgical and radiotherapeutic techniques used in treatment, remained fundamentally unchanged throughout the period covered by this study. The indication for surgery was almost invariably impairment of vision ; rarely, enlargement of the adenoma due to haemorrhage into its substance, or mental or other neurological symptoms of an intracranial space-occupying lesion was the reason for operation. Interference with endocrine function did not form an indication for surgical intervention. When the diagnosis was made of pituitary adenoma with endocrine symptoms alone the patient was referred for treatment by radiotherapy.

The surgical procedure itself also remained essentially unaltered. The tumour was approached by elevation of the frontal lobe and, once exposed, was needled to release any cyst fluid. If as usual the tumour proved to be solid, the false capsule, consisting of condensed pituitary tissue, was incised by diathermy and the contents were evacuated by suction and pituitary rongeur. Infrequently a nodule of tumour was withdrawn in one piece. After inspection of the tumour bed and optic chiasma the bone flap was replaced and the wound sutured. A course of radiotherapy was given as a routine in the early postoperative period ; the few exceptions comprised three patients who had already received preoperative irradiation, and 16 patients surviving operation for longer than six weeks who were not treated for such reasons as age, ill-health, or refusal. The present technique employs a tumour dose of 3,000–4,000 r administered over a period of 28 days, though in the past larger doses have occasionally been used.

Vision

Vision is the most important feature to study in assessing the results of treatment of pituitary adenoma, but the accurate methods of quantification and comparison evolved in recent years (Colby and Kearns, 1962 ; Svien *et al.*, 1965) could not be adopted for the data available in the present study. The preoperative visual acuity was recorded in the case records by Snellen and Jaeger reading type, and the visual fields on charts obtained from the Lister perimeter with a 1-mm. white object at 330 mm. The postoperative vision of the 152 survivors who were examined was tested under similar conditions, except in some instances of domiciliary visit when measurement of the fields by confrontation was necessary. To avoid bias the preoperative record of vision was not studied until the post-

operative examination had been completed. In the case of patients who had died the last record of visual acuity and fields was used for comparison with the preoperative record.

Comparison of the preoperative and postoperative visual acuity presented little difficulty, but assessment of changes in the visual fields was less precise, involving a comparison of the area of the temporal fields. For both visual acuity and fields the result was expressed as improved, unchanged, or worse.

Results

Deaths

The mortality rates were surveyed both in the early postoperative period—that is, at operation or within the six following weeks—and subsequently. Adequate information was obtained from 253 patients, 88 of whom had died between first admission to the neurosurgical unit and the start of the present study. The principal sources of information were the case records and follow-up letters, supplemented in some instances by special inquiries. Particular attention was paid to details of the size and extent of the tumour. Necropsy had confirmed the cause of each early postoperative death and of 23 of the 63 late deaths. Table I shows that among 260 patients there were 25 deaths at operation or within the subsequent six weeks, an operative mortality of 10%. A total of 45 patients (17%) were found to suffer from large or extensive tumours; of these, 15 died at operation or within the subsequent six weeks, a mortality rate of 33%. Ten deaths occurred during this period among the 208 patients with small tumours, an operative mortality of just under 5%.

TABLE I.—*Causes of 25 Deaths Occurring at or Within Six Weeks of Operation*

Intracranial haemorrhage	6
Postoperative swelling of tumour remnants	6
Cerebral oedema and infarction	4
Brain-stem damage	3
Pituitary insufficiency	1
Meningitis	2
Previous subdural haematoma	1
Others	2

The principal operative risk arose from damage to blood vessels or neural structures in the region of the hypophysis; haemorrhage into or oedema of tumour remnants also contributed. Endocrine deficiency was the apparent cause of death in only one instance. Two deaths occurred during the course of radiotherapy.

Six out of 11 patients submitted to a second craniotomy died shortly afterwards. In two instances the patient was so ill that ventriculography alone led to the patient's death. Three of the other patients died from vascular damage, the fourth from trauma to the hypothalamus.

Table II shows the causes of deaths occurring at an interval greater than six weeks after operation. The cause of death was confirmed by necropsy in 23 instances and was suggested by ventriculography in two.

TABLE II.—*Causes of 63 Deaths Occurring More Than Six Weeks After Operation*

Cerebral atrophy, cerebrovascular disease, dementia	20
Radiation damage to cerebrum	6
Carcinoma (gastrointestinal tract 3, genitourinary tract 2)	5
Pituitary insufficiency	4
Pneumonia	3
Trauma	3
Recurrence	1
Astrocytoma	1
Status epilepticus	1
Others	4
Cause unknown	15

One-half of the deaths of which the cause is known resulted from the adenoma or from its treatment; most occurred from causes similar to those responsible for postoperative deaths. Pituitary insufficiency appeared to be the cause of death in four patients and a contributory factor in a further six. Fifteen patients died from causes apparently unrelated to the previous illness, though effects of the adenoma or of treatment were also present and may have played a contributory part. For example, impaired visual or cerebral function contributed to the deaths of three patients (two from burns and one a road traffic accident), while dementia contributed to one patient's death from pulmonary embolism.

Symptoms and signs of endocrine deficiency were present in a considerable number of patients, but pituitary insufficiency appeared to be the cause of death in five only. It is not possible to estimate in how many more it played a contributory part. One patient died after a prolonged postoperative hypotensive episode. Among the later deaths was that of a young man after withdrawal of replacement therapy. The other three patients were elderly men who collapsed with hypothermia during cold weather.

The occurrence of radiation damage to the cerebral hemispheres in certain patients has already been described (McKissock, 1952). During the early years of the present series 10 patients were given radiotherapy in doses now recognized as carrying a risk of radiation damage to nervous tissue. Nine of these patients died between 10 months and seven years after completion of the course. Radiation damage was demonstrated by necropsy in three patients and appeared to be probable on clinical grounds in two more. The tenth patient survived for 22 years but was disabled by lens opacities and by progressive dementia for much of this period.

Postoperative Observation and Survival

The study comprised patients operated on over a period of 25 years. Details of their postoperative survival and of the length of time for which they were observed are given in Table III. The number of patients lost to the study was nine, observed for an average period of four years.

TABLE III.—*Postoperative Observation and Survival*

Period of Observation or Survival after First or Only Operation	No. of Living Patients	No. of Deaths
20+ years	5	1
15–19 „	17	2
10–14 „	42	11
5–9 „	53	13
2–4 „	32	18
Less than 2 years	14	43
	163	88

Tumour Recurrence and Second Operations

It is not easy to determine the frequency of recurrence, since asymptomatic recurrences may not be recognized either during life or after death; also, different patients are observed for varying lengths of time. For these reasons the incidence of recurrence can be estimated only approximately, the figure obtained indicating the frequency with which symptoms of recurrence are recognized.

The presence of a recurrent tumour was proved by necropsy, craniotomy, or ventriculography in 11 patients, and appeared probable on the basis of deteriorating vision in a further six. Thus symptoms of a recurrent tumour occurred in 17 patients out of a total of 226 surviving operation for more than six weeks and maintaining contact subsequently, an incidence of 7.5%. The majority occurred within five years of operation, though the longest interval observed was 17 years.

Recurrence may be treated either by operation or by a second course of radiotherapy. In the present series 14 patients were operated on twice, though not all for the removal of tumour tissue. In three patients no tumour tissue had been identified or removed at the first operation, and the second craniotomy was therefore not undertaken on account of recurrence. The

second procedure was ventriculography or postoperative exploration of the tumour bed in two instances each. The remaining seven patients underwent a second craniotomy each for the removal of a recurrent tumour ; the results were disappointing. Three patients died within 18 months and three became demented ; the best result was obtained in a patient whose recurrent tumour proved too firm for removal.

Vision

Of the 152 survivors examined, visual acuity compared with the preoperative state was improved in 83 (55%), was unchanged in 40 (26%) (including 11 patients with visual acuity better than 6/12 in both eyes before operation), and was worse in 26 (17%) ; in 3 (2%) the classification was indeterminate. The visual fields were enlarged in 88 (58%), were unchanged in 41 (27%), and were reduced in size in 20 (13%): in 3 (2%) the classification was indeterminate. In 76 unexamined patients (not all of them survivors) treatment was followed by improvement in vision in 42 (55%), by no change in 18 (24%), and by deterioration in 16 (21%).

It was found that most patients held a more optimistic opinion about their eyesight than examination and the evidence of their relatives showed to be justified. Accordingly the patient's opinion was discounted unless it could be supported by objective evidence of increased capacity, and the assessment of visual function was made on the basis of the physical findings alone. The results therefore reflect a critical attitude to the results of operation and show that the changes in both visual acuity and visual fields after operation were similar ; over one-half of the patients had objective evidence of improved vision, and no further deterioration of vision occurred in one-quarter. The results referring to patients who were not examined in the present study resemble the foregoing. In most patients improvement was a gradual process over a period of several months after operation, but wide variations in the rate of recovery were observed and it was occasionally immediate. The less extensive and more recent the onset of visual impairment, the greater chance of successful treatment, which was also greatest in respect of bitemporal field defects ; atypical field loss carried a less favourable prognosis, since it indicated lateral extension of the tumour.

Other Neurological Features

Headache, present to some degree in two-thirds of patients before operation, was almost always relieved by treatment. Epilepsy occurred in 2.3% of patients preoperatively and in 4.7% of the survivors. Dementia was rarely recorded before operation, but some impairment of cerebral function occurred in approximately half those patients examined ; only in 17 instances was it severe enough to interfere with the patient's employment or family life. Other mental illness occurred in only three of the examined patients. Hypothalamic injury, as judged by the presence of diabetes insipidus, occurred in one patient before operation and in 10 subsequently, in each of which it was a temporary complication requiring treatment for six months at most.

Cranial-nerve lesions were especially common in patients with extensive or haemorrhagic tumours, and were generally relieved by operation. Only in respect of olfaction and of hearing was cranial-nerve function worse after operation than before, owing to the effects of surgery and of radiotherapy respectively.

Endocrine Function

The findings of an investigation into the state of endocrine function in patients treated for pituitary adenoma form a separate communication (Elkington *et al.*, 1967).

Discussion

Comparison between series of patients treated for pituitary adenoma is often complicated by the use of a variety of therapeutic techniques, by differing diagnostic criteria, and by the nature of the tumour treated. The present report appears to be the first of its size to be made on patients in this country, and to be exceeded in the number of patients treated surgically only by the series of Henderson (1939) (338 patients) and of Bakay (1950) (292 patients).

The findings of Jefferson (1940) and of many subsequent workers regarding the relation between tumour size and operative risk have been confirmed. Tumours with large suprasellar or parasellar extensions comprised 18% of the present series but accounted for 33% of the deaths at operation or within the subsequent six weeks, compared with a mortality rate of 5% in patients with small tumours. Comparable mortality figures in other reports are 36% and 2% respectively (Jefferson, 1940) and 35% and 6% respectively (Bakay, 1950). In most instances death resulted from the traumatic effects of operation upon the cerebrum, brain stem, or blood vessels, the contribution of hypopituitarism being slight in terms of mortality but considerable in terms of morbidity. In support of this is the finding of Troen and Rynearson (1956) that the routine administration of replacement therapy before operation did not improve the mortality rate, though the incidence of postoperative complications was reduced. Deaths occurring more than six weeks after operation also resulted chiefly from the effects of tumour or treatment, hypopituitarism playing only a slightly larger part as a cause of death than in the case of mortality within six weeks of operation.

Tumour recurrence was observed in 7.5% of patients, a figure in agreement with that recorded by Ray and Patterson (1962) but lower than those reported by Henderson (1939) (56% before and 13% after the administration of routine radiotherapy). This complication usually occurs within five years of operation, but may occasionally not produce symptoms until a much greater period has elapsed (for instance, 17 years in the case of one well-documented patient in the present series).

The results of operation in improving vision were similar both in patients examined for this series and in those not examined, whether visual acuity or fields were employed for the comparison. In each instance improvement occurred in from 55% to 58% of patients, while in another 24% to 27% there was no further deterioration. Among survivors vision was worse after operation in 13% to 17%, while in those not examined (chiefly owing to death) the proportion was a little higher (21%). The methods adopted by previous workers in assessing the results of treatment differ slightly, but their findings are similar. Henderson (1939) observed improvement in 65% of patients six months after operation, though after a longer period the number of tumour recurrences reduced the proportion of favourable results. Bakay (1950), using different criteria, found that acuity and fields were improved in 53% and 59% respectively. Mogensen (1957) reported similar figures, while Gurdjian *et al.* (1955) and Ray and Patterson (1962) found improvement in 66% and 75% respectively. The incidence of further deterioration in vision in the present series is higher than in some other reports but resembles that noted by Svien *et al.* (1965). The explanation may be the longer average postoperative interval which elapsed in the present series. It is noteworthy that Svien and his colleagues used the accurate method for the assessment of vision advocated by Colby and Kearns (1962).

Treatment was particularly successful in relieving headache, but less so in improving lesions of the oculomotor and abducent nerves. Both impairment of olfaction and that of hearing were more common subsequently, the latter as a result of irradiation, while the rise in the incidence of epilepsy from 2.3% to 4.7% resembles the finding of Poppen (1963). Hypothalamic injury, as shown by diabetes insipidus, occurred in only one patient before operation but transiently in 10 patients after operation.

Summary

The results of treatment of 260 cases of pituitary adenoma by a combined surgical and radiotherapeutic technique have been reviewed: all operations were performed through the transfrontal route, and all but 19 patients surviving for more than six weeks received irradiation subsequently.

The overall mortality rate at operation and within the subsequent six weeks was 10%. Among the 45 patients (18% of the total) with large or extensive tumours the operative mortality rate was 33%, while among the remainder it was just under 5%.

The most frequent cause of death at or within six weeks of operation was trauma of or haemorrhage into the brain, while cerebral degeneration was the commonest cause of later deaths. Pituitary insufficiency alone caused only five out of the total of 88 deaths.

Symptoms of a recurrent tumour were recognized in 7.5% of survivors. Most occurred within five years of operation, but occasionally the interval was much longer. Second operations, whether or not performed for recurrence, obtained indifferent results.

Vision was improved by treatment in a little over one-half of the patients, and was unchanged in one-quarter. Deterioration occurred in about 15%. Headache was usually relieved by operation, but lesions of the first and eighth cranial nerves were more common after treatment, owing to surgery and radiotherapy respectively.

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Driving after Temporal Lobectomy for Epilepsy*

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The subject of epilepsy and driving licences was discussed in September 1965 at an International Symposium held in Vienna (*Social Studies in Epilepsy*, 1966), and again in 1966 at a combined meeting of the British Branch of the International League Against Epilepsy and the British Epilepsy Association (*British Medical Journal*, 1966). It seems clear that the application of the existing law in this country to those patients whose epilepsy is controlled is unsatisfactory, and we therefore propose to describe some findings gained during follow-up studies of patients whose epilepsy has been controlled by anterior temporal lobectomy, since they highlight the difficult nature of the problem.

The legal position of the epileptic who wishes to drive in this country seems at first sight to be clear enough. In completing the application form (D.L.I.R.—Revised—1965) he must answer the following question: "Do you suffer from either of the following diseases or disabilities ? . . . (1) Epilepsy ; (2) Sudden attacks of disabling giddiness or faintness." The penalty for knowingly making a false statement may be a fine not exceeding £100 or imprisonment for a term not exceeding four months, or both.

As Turner (1966) pointed out, difficulties arise from the interpretation of words "suffering from epilepsy," and also from the fact that driving licences in this country are not issued by a central Government authority but by local authorities, who interpret these words variably. The ideas of laymen also vary, and we have found that quite often patients who have become fit-free after operation decide for themselves that they are no longer "suffering from epilepsy," and apply for and obtain a driving licence in the ordinary way without seeking medical or legal opinion. The licensing authorities have from time to time been given advice on the subject. Thus some years ago a committee of the Royal College of Physicians of London recommended that an applicant should have been fit-free for five years, for the last two of which he should have been off medication. In 1961 the Ministry of Transport sent a memorandum stating, *inter alia*: "The Department has received advice that epilepsy should be regarded as a continuing liability to recurrent epileptic attacks. It follows that a person who has in the past had one or more attacks of convulsions, or of disturbance of consciousness, in circumstances which are unlikely to recur, need not necessarily be regarded as suffering from epilepsy. . . . In any case of doubt the licensing authority will no doubt consult the local county council or county borough medical officer of health. . . ." There is also provision for a dissatisfied applicant having his case heard at a magistrate's court, a course of action with its inherent publicity which few individuals care to face.

Present Position

During the past 14 years about 200 patients with intractable temporal-lobe epilepsy have been operated on in the Guy's–Maudsley Neurosurgical Unit. Detailed studies of the operative

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