THE RESULTS OF 300 PITUITARY ADENOMA OPERATIONS (PROF. HERBERT OLIVECRONA'S SERIES)

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Between the years 1929 and 1947, 292 patients with verified pituitary adenoma were treated at the Serafimerlasarettet in Stockholm and the number of operations performed was 300. The detailed follow-up of almost all patients allows an accurate analysis of the value of these operations and of the postoperative prognosis. There is only one similar follow-up study in the medical literature, Harvey Cushing's 338 pituitary adenoma cases as reported by Henderson in 1939.

The 292 cases of pituitary adenoma observed in the Olivecrona series represented 8.9 per cent of the total number of verified brain tumors. On the other hand, the 338 corresponding cases in Cushing's series represented 17.8 per cent of a total of 1923 brain tumors—a larger percentage.

Histologically, 232 of the adenomata have been classified as chromophobe (with 246 operations); 55 as acidophil or mixed but with an overwhelming majority of the acidophil elements (52 op.); 2 as basophil (2 op.); and 3 as malignant (3 op.).

The maximum incidence of chromophobe adenomata occurred in patients between the ages of 50–54, much higher than in Cushing's series. Twenty-six patients were over 60 years of age. The age incidence of patients with acidophil tumors was lower, about 30 years of age, and only 1 of them was over 60.

In 55 (33.9 per cent) of the cases of chromophobe adenoma and in 18 (35.3 per cent) of the cases of acidophil adenoma, the patients had received varying periods of x-ray treatment during the years or months prior to operation.

The types of operations performed are recorded in Table 1. This table does not include 13 re-explorations performed shortly after primary operation for actual or suspected blood clot formation or edema of the frontal lobe. The re-explorations were followed by resection of the frontal lobe in 4 cases, a rare procedure in the primary operations. Primarily it was performed in only 4 cases, in which the approach to the big extrasellar adenomata was not possible by other means.

The surgical approach was transfrontal in 241 chromophobe and 45 acidophil adenoma cases (95.3 per cent of all operations), and transsphenoidal in 5 chromophobe and 9 acidophil cases (4.7 per cent). A fundamental difference exists, therefore, between our cases and Cushing's statistics, the transfrontal

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Technic having been used in almost all of our pituitary operations, whereas most of Cushing’s patients were operated upon transsphenoidally (64.6 per cent of the chromophobe and 90 per cent of the acidophil adenomata).

There were 28 (11.3 per cent) postoperative fatalities after 246 chromophobe adenoma operations, 4 (9.5 per cent) after 52 acidophil, 2 after 3 malignant, and none after the 2 basophil operations. The results improved with time, however, and the series of 30 acidophil adenomata operated upon in the last 10 years had the remarkably low mortality rate of 3.3 per cent. All patients who remained in the hospital and died there from any cause are included in these figures. The postoperative mortality rates of Cushing’s 338 cases were 4.9 per cent for the chromophobe and 8.6 per cent for the acidophil, without any essential difference between the transsphenoidal and the transfrontal operations. Grant’s series (143 pituitary adenomata) showed a mortality rate of 11.5 per cent for the transsphenoidal and 9.5 per cent for the transfrontal route. It is obvious that there are fewer postoperative deaths in cases of small intrasellar growths and that the mortality rate is much higher when there is extrasellar extension. Jefferson reports 2 per cent mortality in the first and 33 per cent in the second group. In our series there were 14 fatalities (35 per cent) after operations for chromophobe adenomata with extension (40 cases), and 14 deaths (6.4 per cent) after operations for tumors without extension.

The causes of deaths are listed in Table 1.

Most fatalities are due to the incomplete removal of large adenomata invading the hypothalamus and the 3rd ventricle. The extirpation, however, of such tumors is hardly possible. Hyperthermia without any other symptom followed by death has been observed in 3 cases. Hyperthermia is a well known factor in pituitary operation statistics and is supposed to be the sign of a hypothalamic crisis, although its origin is not clear.

**EXTRASELLAR EXTENSIONS**

It is known that a certain number of pituitary adenomata tend to extend into the intracranial chamber. According to the estimation of Henderson

<table>
<thead>
<tr>
<th>Types of Operations Performed</th>
<th>Chromophobe</th>
<th>AcidophIl</th>
<th>Basophil</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracapsular enucleation</td>
<td>232 (ex. 24)</td>
<td>45 (3)</td>
<td>2 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>(a) transfrontal</td>
<td>229 (22)</td>
<td>35 (2)</td>
<td>2 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>(b) transsphenoidal</td>
<td>5 (0)</td>
<td>10 (1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Partial extirpation</td>
<td>10 (6)</td>
<td>1 (0)</td>
<td>—</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>3 (0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Exploration</td>
<td>1 (0)</td>
<td>2 (1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Subtemporal decompression</td>
<td>—</td>
<td>1 (0)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
and Jefferson,\textsuperscript{8} the incidence of extrasellar extension is about 14 per cent.

Extension in the \textit{cavernous sinus} was present in 15 chromophobe and 1 malignant adenomata (6.8 per cent). In these cases the laterally growing neoplasm maintains a permanent and increasing pressure on the medial wall of the sinus or invades it and injures the structures that it contains, particularly the oculomotor nerve, as described by Boschi and Campailla,\textsuperscript{1} Weinberger, Adler and Grant,\textsuperscript{10} and Jefferson.\textsuperscript{8} The first symptom is usually a slight disturbance in coordination of the ocular muscles and diplopia (2 cases) due to weakness of the 3rd nerve. Palsy of the nerves leading to the muscles of the eye occurs in more advanced cases and varies largely in ex-

\begin{table}
\centering
\caption{Causes of Death}
\begin{tabular}{lccc}
\hline
 & Chromophobe & Acidophil & Malignant \\
\hline
Partial removal, followed by increased intracranial pressure & 9 & 3 & 1 \\
Pituitary insufficiency & 4 & -- & -- \\
Postoperative clot formation & 2 & 1 & -- \\
Hemorrhage into ventricles & 1 & -- & -- \\
Thrombosis of anterior cerebral artery & -- & -- & 1 \\
Hyperthermia (hypothalamic crisis) & 2 & 1 & -- \\
Meningitis & 1 & 1 & -- \\
Pneumonia & 2 & -- & -- \\
Cardiac insufficiency & 1 & -- & -- \\
Pulmonary embolism & 1 & 1 & -- \\
Miliary tuberculosis & 1 & -- & -- \\
Scarlet fever, endocarditis & 1 & -- & -- \\
\hline
\end{tabular}
\end{table}

tension and severity. In our series partial or complete oculomotor nerve palsy was observed in 11 cases, paralysis of the trochlear nerve in 2, and paralysis of the abducens nerve in 2. It is easy to understand that the extension of an adenoma in the cavernous sinus is a sign of asymmetrical growth and therefore causes homonymous hemianopia or only one-sided temporal hemianopia more frequently than the usual type of adenoma. The lateral extension does not always mean that the neoplasm has also extended upwards; a lesion of the nerves of the cavernous sinus, without injury of the optic nerve, has been observed in some cases.

Protrusion of the eyeball on one side, as occurred in 2 of our patients, is also caused by the invasion and the resulting venous congestion of the cavernous sinus. It is diminished after removal of the tumor.

Jefferson thinks that the existence of symptoms originating in the structures of the cavernous sinus does not mean a poor prognosis unconditionally but he classified the invading type of these adenomata as malignant. In our cases, however, there was only 1 that could be classified as malignant by the microscopic picture; it resulted in total 3rd and 4th nerve palsy on the left side. It is remarkable that 3 of the 16 patients have been operated upon later for recurrence of symptoms, a moderately high rate of recurrence, but
on the other hand, it is difficult to decide if this was due to the malignancy of these neoplasms or only to the fact that it is extremely difficult to remove an adenoma completely from the wall of the cavernous sinus. The number of postoperative fatalities in this group with extension into the cavernous sinus was not higher than with the usual adenoma (2).

Obstruction of the internal carotid artery can be caused also by extension in the lateral direction, as observed in 2 of the chromophobe cases. In 1 the neoplasm grew upwards, following the path of the artery. In the other the adenoma surrounded the left carotid artery and obstructed it, later causing disturbances in cerebral circulation, slight hemiparesis on the right side, facial weakness, slight aphasia and agraphia.

Another sign of lateral extension is invasion into the cave of Meckel. Trigeminal pain or anesthesia due to this extension (described by Jefferson as a sure sign of malignancy) was observed in 3 cases, 2 chromophobe and 1 acidophil. In 1 case autopsy revealed a large tumor growing upwards into the 3rd ventricle and extending widely on the base of the skull, infiltrating the semilunar ganglion.

One example of marked temporal extension can be presented in our series. The extension to the right side was shown by atrophy of the right optic nerve with total blindness, while the left optic nerve and vision were normal with but a slight temporal shrinking of the visual field. There were, in addition, paralyses of the right oculomotor and hypoglossal nerves, and a slight hemiparesis on the left side.

Although there were several adenomata among the chromophobe and malignant cases that showed infiltration into the sellar floor, erosion of the base of the skull and extension into the nasopharynx could not be observed. Another rare pathway of extension is backwards and downwards, the adenoma growing below the tentorium (White and Warren12). In 1 of our cases the occipitally growing tumor compressed the cerebral peduncles and injured the pyramidal tracts.

The projection of the adenoma upwards into the 3rd ventricle, the so-called hypothalamic extension, is of great prognostic importance. Compression of the hypothalamus and invasion of the 3rd ventricle frequently make the outcome of operation unfavorable. The most striking examples were represented by those 14 adenomata (11 chromophobe, 2 acidophil and 1 malignant, altogether 4.7 per cent) that protruded into the 3rd ventricle and filled it almost completely, blocking the circulatory pathway of the cerebrospinal fluid, with resultant hydrocephalus and symptoms of increased intracranial pressure. Some of the rare cases of papilledema have been found in connection with these neoplasms. In 1 of our patients the tumor did not remain localized to the 3rd ventricle but extended upwards in the right lateral ventricle through the interventricular foramen. The postoperative mortality rate of this group was high (71.4 per cent).

In less advanced cases hypothalamic symptoms were caused by compression of this region. Polydipsia and polyuria (alteration of the supraoptic
nucleus and its connections) were present in 20 cases of chromophobe tumors (8.5 per cent) and drowsiness occurred in 14, the latter originating probably in injury of the hypothalamic sleep-centers (Jefferson). There are three different periods in pituitary adenomata in which hypothalamic symptoms can develop. A preoperative lesion is due to direct pressure on the hypothalamic nuclei by the upwardly extending tumor; the lesion diminished or disappeared after removal of the adenoma with but 1 exception. Another type of disturbance occurs in the early postoperative period, lasts some days or weeks and is usually transitory. Good effect is to be expected from treatment with posterior lobe extracts. In this period the symptoms are caused probably by surgical manipulation and injuries of the hypothalamus. The third group consists of cases in which the symptoms start years after the operation and suggest a recurrence of the adenoma. The mortality rate of patients with primary polydipsia and polyuria is high and the late results of operation are not favorable. Four of the patients died following enucleation of the tumor, and 5 others within 5 years, altogether 45 per cent of this group. Transitory postoperative polydipsia and polyuria were observed in 6 cases, but in none of these became permanent.

Polydipsia and polyuria were found in 12 cases (22.7 per cent) of acidophil adenoma. There were 3 postoperative fatalities, and 2 other patients died within the next 2 years (together 41.6 per cent). Postoperative transitory polydipsia developed in 1 patient; the absence of this complication in the others can be explained by the fact that several patients were operated upon through the transsphenoidal approach, a method that certainly does not injure the hypothalamus.

Two patients with chromophobe adenoma suffered from epileptic seizures and 3 showed mental disturbances. These signs are not frequent in connection with adenomata of the pituitary body, but, if present, are a danger signal indicating that the tumor is expanding widely beyond the sella turcica (Jefferson; White, Liu, and Mixter).

The estimation of the size and location of the extrasellar extension makes the operative planning easier. Encephalography, especially the filling with air of the basal cisterns, is of great help (Figs. 1, and 2, and 3).

OCULAR SYMPTOMS

Visual Acuity

Chromophobe Adenomata. The preoperative examinations showed that the vision of 159 patients (68.5 per cent) was affected in both eyes. Unilateral blindness was present in 17 cases and bilateral in 1. The operative mortality rate of this group was 10.7 per cent (17). The vision of one eye only was diminished in 63 cases (27.2 per cent); in 8 cases there was blindness of one eye. The mortality of this group increased to 17.4 per cent (11). Finally, normal vision of both eyes was recorded in 10 patients (4.3 per cent); none of them died following operation. The small number of this last category in-
Fig. 1. Case S. G. M. Subfrontal extension of adenoma. Note upward bulge of the floors of both anterior horns. The 3rd ventricle is dilated, deformed and displaced to the right.

Fig. 2 (left). Case C. O. F. Suprasellar extension causing deformation and displacement of 3rd ventricle and of basal cisterns upwards and backwards.

Fig. 3 (right). Case E. A. L. Suprasellar extension. Note impression of the floors of the anterior horns. The anterior part of the 3rd ventricle is deformed and displaced upwards and backwards, and the slightly filled interpeduncular cistern is pushed backwards.

dicates that patients with chromophobe adenoma are rarely operated upon only because of their endocrine hypofunctions or general symptoms, the main surgical indication still being the visual deterioration.

In 63 cases (27.6 per cent) the optic discs were normal on both sides or showed only a slight temporal decoloration which could not be diagnosed with certainty as pathologic. Unilateral optic atrophy was found in 48 patients (21 per cent), and bilateral in 117 (51.4 per cent). The postoperative
mortality rate was higher in this latter group (17 per cent) than in the two former (7.9 per cent and 6.2 per cent, respectively).

The early results of operation have been analyzed on the basis of several visual examinations 2–3 weeks after operation. The degree and speed of the visual improvement is related to the preoperative condition of the optic nerves, although a slight decoloration of the papillas is not always a sure sign of atrophy. As described by de Martel, Monbrun and Guillaume, an early decoloration could be the consequence of ischaemia of the optic nerve due to compression of its blood vessels by the adenoma. In these cases the removal of the tumor is followed by a quick recovery because of the normalization of the blood supply, and the vision and visual fields become normal.

Early control examinations were performed on 202 patients with chromophobe adenoma whose visions were found impaired before surgical intervention. Improvement in vision of both eyes was found in 46 (completely normal vision in 11), and of one eye in 36 (normal in 8). Consequently the operation resulted in immediate visual amelioration in 40.6 per cent. Remarkably enough, the number of these cases is exactly the same as the number of cases in which the optic discs showed no pathologic alteration preoperatively or only a slight temporal ischaemia. In 7 cases visual acuity increased on one side and diminished on the other after operation. In 21.2 per cent of the cases surgical intervention caused visual deterioration in both eyes in 25 patients and in one eye in 18. Nine patients became amaurotic in one eye, and 1 in both, due to the immediate effect of the operation; all of them had had very poor vision before surgery. The cause of such blindness is probably the injury of the optic nerves done at the transfrontal manipulation and enucleation of the adenoma, and in some cases suprasellar clot formation. Similar cases were observed by Henderson in the Cushing series only after operations by the transfrontal approach. In 60 cases (29.7 per cent) removal of the adenoma had no effect on the diminished vision in the early postoperative period.

Examination of the patients 2 years or more after operation furnished supportive data for evaluating the late results of surgical intervention. Of the patients who had had chromophobe adenoma, 164 were examined 2 years after removal of the tumor. They were divided into five groups on the basis of their vision: (1) good vision bilaterally (visual acuity 0.8–1.0). There were 35 patients in this group (21.3 per cent). (2) Reduced visual acuity, but still with full ability to work. This group comprises those patients who had moderate loss of vision in both eyes or who had normal vision in one eye but very reduced vision in the other—62 cases (37.8 per cent). (3) Bilaterally impaired vision causing diminished ability to work—38 patients (23 per cent). (4) Poor vision, finger counting, perception of hand movement, light, etc., and unable to work—23 patients (14.2 per cent). (5) Blindness—6 patients (3.6 per cent).

Consequently, the late results with regard to visual acuity were good or satisfactory in 59.1 per cent. Visual acuity was reduced in 23 per cent. The
patients lost their self-supporting ability in 17.8 per cent. It is rather difficult to compare these data with those of Henderson because he used a different classification based upon the ophthalmological examination as early as the time of discharge from hospital. Later observation, however, gives more reliable and permanent data for judging the final outcome of operation. Nevertheless, the results of our series are in accordance with those of Cushing. Henderson stated that 68 per cent of their patients left the hospital fully able to work as regards vision. Cushing reported that 21 per cent of the transfrontally operated patients regained normal vision and visual field (but only 9 per cent of transsphenoidally operated), which accords with the 21.3 per cent of the first group of our classification.

**Acidophil Adenomata.** The preoperative examination of 55 patients revealed bilaterally diminished vision in 24 cases (43.6 per cent), unilateral impairment in 19 (34.5 per cent), and normal visual acuity in 11 (21.9 per cent). The optic discs did not show any significant sign of atrophy in 57.4 per cent of the cases; atrophy of one of the papillae was observed in 32 per cent, and bilateral decoloration only in 10.6 per cent. Papilledema of both discs was found in 7 patients, more often than in those with chromophobe adenoma. The postoperative findings of 33 acromegalic patients with impaired vision showed the following distribution: 10 were improved in both eyes (30.3 per cent), 10 in one eye only (30.3 per cent), 11 did not change (33.3 per cent), and further deterioration was observed in but 2 cases. The conclusion is, therefore, that the early results are more favorable in acidophil adenoma cases than in chromophobe. The late results with regard to vision are also better. Two years after removal of the tumor from 29 acromegalic patients, 16 were classified in the first group (55.2 per cent), 11 in the second (37.9 per cent), and 2 (6.9 per cent) had reduced ability to work due only to ophthalmic symptoms. None of the patients became blind or suffered such deterioration of vision that they became unable to support themselves.

**The Visual Fields**

**Chromophobe Adenomata.** Of the 232 patients, 147 had bitemporal hemianopia (63 per cent) in the form of complete hemianopia, upper quadrantic defect, temporal constriction or temporal scotoma of the visual fields. That is in accord with Henderson's observations on Cushing's series (65 per cent). Henderson also included in this group, however, those patients with a history of bitemporal constriction of the visual field in whom the visual defect had progressed to blindness in one eye at the time of admission to hospital. Our classification was based entirely upon perimetric findings at the time of surgical intervention.

Removal of the adenomata resulted in complete normalization of both visual fields in 22 patients (14.9 per cent), bilateral improvement in 35 (23.8 per cent), normalization in one eye without change in the other in 13 (8.8 per cent), and unilateral improvement in 8 (5.4 per cent). The constriction of both visual fields progressed after operation in 7 cases and on one side
only in 5. In addition to the 52.9 per cent of amelioration and 8.1 per cent of deterioration, the hemianopia was recorded as unaltered by the operation in 29.5 per cent (43 cases). The postoperative mortality rate of patients with bitemporal hemianopia was 9.5 per cent (14 fatalities).

One eye was blind and the other affected in 36 cases of chromophobe adenoma (15.5 per cent). The operation improved the visual field in 12 cases (33.3 per cent) but did not improve it in 17 (47.2 per cent), and the visual field became worse in 2 cases. There were 5 postoperative fatalities (13.8 per cent).

In 22 cases only one eye was affected by the tumor (9.4 per cent). The effect of the removal of the adenoma in these cases was in general good. Nine patients improved (40.9 per cent); the visual fields of 7 of them became completely normal. The constriction continued in 3 cases; 5 did not change. The postoperative mortality rate was 22.7 per cent (5 cases).

Homonymous hemianopia was present in 7 cases (3 per cent), a rare occurrence in comparison with the 10 per cent of the Cushing series. None of these patients was improved by the operation; in 2 the progression of symptoms could not be arrested, 3 remained unaltered, and 2 died (28.5 per cent mortality).

Normal visual fields occurred in but 9 patients (3.8 per cent). There were no postoperative fatalities in this series. Bilateral blindness was present in 3 patients, of which 1 died. There were 4 instances in which the visual field of one eye was normal and the other eye was blind.

Summarizing these data it can be stated that the best chance for recovery from the visual field defects and the best operative prognosis are offered by the cases with bitemporal hemianopia. Very good results were obtained in those patients who had only upper quadrantie anopia, partial temporal defect or scotoma. The excellent results in patients with normal visual fields are of much less practical importance because of the rare occurrence of such cases. Homonymous hemianopia and other atypical types of defect that indicate deviation of the adenoma from the midline and its lateral extension increase the operative mortality rate and are followed often by disappointing results.

**Acidophil Adenomata.** Out of 53 acromegalic patients bitemporal hemianopia was present in 22 (41.5 per cent). Extirpation of the adenoma reestablished normal visual fields in both eyes in 8 cases, and improved them in 3 patients bilaterally and in 3 unilaterally (altogether 63.7 per cent). The operation had no effect in 5 cases. There were 3 postoperative fatalities (13.6 per cent).

The visual fields were normal in 8 cases (33.9 per cent); the mortality rate of this series was only 5.5 per cent.

Normal visual field of one eye and temporal defect of the other was observed in 9 cases (16.9 per cent); one improved and the others remained unaltered by the operation.

Homonymous hemianopia was present in 1 case, temporal hemianopia
of one eye with blindness of the other in 2 cases. One of these patients showed a striking improvement on the blind side after removal of the tumor.

ENDOCRINE FUNCTIONS

The endocrine deficiency observed with chromophobe adenomata is due to compression and damage of the pituitary cells by the tumor, and consequently the removal of such an adenoma is rarely followed by improvement in the endocrine functions. The clinical features sometimes become even worse because of the inevitable destruction of the remaining secretory tissue of the gland at the operative manipulation. For this reason, even successful surgical interventions can be followed by complete pituitary insufficiency. However, the removal of an acidophil adenoma, composed of highly active secretory cells, sometimes alleviates symptoms of hyperpituitarism.

Sexual Functions. There were 61 females with chromophobe adenoma between the ages of 15 and 50, and only 9 of them (14.7 per cent) had regular menstruation before operation. The menstruation was irregular in 5 cases and was absent in 47 (77 per cent). Ten patients regained their menses following operation (21.3 per cent of those with preoperative amenorrhea), but only 5 of them regularly and for a longer period. The operation resulted in menopause in 2. Among the 30 female patients suffering from acidophil adenoma there were 8 (26.6 per cent) with regular and 3 with irregular menstruation, and amenorrhea was present in 19 (63.3 per cent). Of the patients with preoperative amenorrhea 16 per cent regained regular menses after removal of the tumor; 1 of them became pregnant several years later and had normal delivery.

There were 119 males with chromophobe adenoma between the ages of 18 and 60 years. Sexual functions were altered in about 46 of them (88.6 per cent) before operation and reduced in 30 (25.2 per cent). Impotence and loss of libido were recorded in 43 cases (36.2 per cent). After operation sexual functions returned in 1 and improved in 2 others; however, in 2 cases they were completely lost. There were 19 males with acidophil adenoma in this age group, and in only 4 instances was impotence recorded (21 per cent); normal function was present in 8 (39.5 per cent) and was reduced in 8 other patients. The operation had no effect upon sexual functions in all but 1 case.

Loss of sexual functions, in Henderson’s opinion, is a deprivation syndrome due to compression of the normal anterior-lobe cells by the enlarging tumor, and is not due to the activity of its secretion. Therefore the syndrome is more striking with intrasellar growths, and it occurs later with extrasellar adenomata, which compress the normal pituitary cells only in a later period.

Blood Sugar. It is well known that diabetes is often present in cases of acidophil adenoma (in 25 per cent, as reported by Davidoff and Cushing); blood sugar concentration is usually high and tolerance diminished, as compared with the low blood sugar level of those with chromophobe adenoma. Out of 90 patients with chromophobe adenoma, 80 had a blood sugar concentration below 100 mg. per cent and diabetes was observed in only 1. This
patient had marked diabetes, glycosuria, and a blood sugar level over 200 mg. per cent; however, complete recovery in carbohydrate metabolism occurred after removal of the tumor. On the contrary, diabetes developed in 3 patients, 1, 3 and 8 years, respectively, after enucleation of a chromophobe adenoma.

In 23 cases of acidophil adenoma the blood sugar concentration was examined; it was over 100 mg. per cent in 11, including 5 cases of marked diabetes. One of the diabetics recovered after operation, 1 remained unaltered, while progression of symptoms occurred in 2.

It is almost impossible to analyze the results of the operations with regard to blood sugar changes, because of spontaneous variations and remissions, characteristics of the acromegalic diabetes.

**Basal Metabolism.** Increased metabolic rate has been observed in many cases of acromegaly (Cushing and Davidoff) but chromophobe adenomata are usually associated with subnormal metabolism. Goiter is a quite common feature in acromegalia; the hyperthyreosis often improves following the removal of an acidophil adenoma. Out of 180 cases of chromophobe adenoma in which basal metabolic rate was determined, 133 (73.9 per cent) revealed a value below 0 (29 of them below –20 per cent). The hypothyroidism in the chromophobe cases is probably due to diminished secretion of thyrotropic hormone by the compressed anterior lobe and, being a deprivation symptom, usually remains unaltered by the operation, sometimes even becoming worse. In such cases surgical intervention can cause myxedema, sometimes years after the operation.

The basal metabolic rates in the acidophil adenoma cases were as follows: in 11 cases below 0 (26.8 per cent), and in 30 above 0 (73.2 per cent), 7 of them being over +20 per cent. Goiter was present in 6 patients.

**Blood Pressure.** Among the patients with chromophobe adenoma (224 examined), 66 (29.4 per cent) had a systolic pressure between 80 and 120 mm., 132 (58.8 per cent) between 120 and 160, and 26 (11.8 per cent) above 160 mm. On the other hand, of the 52 with acidophil adenoma only 10 (19.2 per cent) had a pressure below 120 mm., while in 20 (57.7 per cent) it was between 120 and 160, and in 12 (23.1 per cent) above 160 mm.

Removal of the tumor does not influence the high blood pressure. It remains unaltered in some cases during the following years; frequently, however, it shows progression, especially in cases of acidophil adenoma, sometimes leading to death from cerebral hemorrhages.

**LATE RESULTS OF THE OPERATIONS**

**Chromophobe Adenomata.** Accurate follow-up of almost all patients who lived in the countries of Scandinavia has been possible, and examinations, or reports written by their doctors or themselves, have been obtained yearly. However, records of the late results of those who came from other countries have sometimes been incomplete, especially during the years of war.

Of the patients with chromophobe adenoma who were operated upon in
the past 18 years and survived the operation, 130 are still living, 9 of them after further operation for recurrence of the neoplasm. The death of 40 patients was reported: 8 died from recurrence of the tumor, 5 from endocrine insufficiency, 18 from incidental causes, and 9 from unknown conditions. It was possible to follow 176 patients over 2 years after removal of the adenoma. The ability to work and the question of self-support was determined individually, the age and profession of each patient being taken into consideration. There were 96 fully able to work (54.5 per cent) after the 2-year period. Representatives of various mentally and physically exerting professions were found in this series (engineer, navy officer, horseman, sportsman, woodcutter, etc.), demonstrating that a successful surgical intervention can be followed by complete mental and physical restitution. The ability to work was reduced in 48 cases (27.2 per cent) for various reasons, in 33 being due to loss of vision. Reduced vision was reported also by some other patients in

<table>
<thead>
<tr>
<th>Elapsed Time after Operation</th>
<th>Maximum Number of Patients</th>
<th>Untraced</th>
<th>Alive</th>
<th>Per Cent Alive</th>
<th>Died</th>
</tr>
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<tr>
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<td>195</td>
<td>13</td>
<td>147</td>
<td>80.8</td>
<td>35</td>
</tr>
<tr>
<td>4 years</td>
<td>158</td>
<td>11</td>
<td>111</td>
<td>75.5</td>
<td>36</td>
</tr>
<tr>
<td>6 years</td>
<td>196</td>
<td>14</td>
<td>89</td>
<td>79.4</td>
<td>23</td>
</tr>
<tr>
<td>10 years</td>
<td>74</td>
<td>10</td>
<td>49</td>
<td>76.5</td>
<td>15</td>
</tr>
<tr>
<td>14 years</td>
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<td>12</td>
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<td>9</td>
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<td>18 years</td>
<td>2</td>
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</tbody>
</table>

whom the reduced ability to work was due mainly, not to reduction in vision, but to other reasons—in 6 cases, to impaired mental condition, weakness, or indifference; in 4, to hypertension; in 2, to epileptic seizures; in 2, to endocrine disturbances (myxedema, diabetes), and in 1, to persistent strong headaches. Inability to be self-supporting was reported by 32 patients (18.3 per cent)—in 24 cases due to loss of vision or blindness, in 6, to mental symptoms, headaches, and apathy, in 1, to cerebral hemorrhage, and in 1, to frequent seizures.

It has been supposed that the long postoperative survival periods in our series (Table 3) are due to the transfrontal enucleation of the adenomata. Although this type of operation has a higher mortality rate, it represents a much more radical removal of the neoplasm and consequently there are fewer late fatalities from recurrence than after the transsphenoidal operation. Furthermore, another important factor in the long survival periods is the postoperative x-ray treatment which was given routinely with but very few exceptions. A definite improvement in the late results of operation when followed by x-ray treatment was described by Henderson.

Acidophil Adenomata. Of the patients operated upon for acromegalia, 19
have been reported to be still alive and 14 others died. The cause of death
was splanchnomegaly and dilatation of the heart in 4 cases; hypertension,
arteriosclerosis, cerebral hemorrhage in 3, diabetes in 2; recurrent tumor
in 2; and progressing pituitary insufficiency and adynamia in 1 (autopsy
revealed an old clot at the site of the pituitary body and hemorrhages in the
hypothalamus). In 2 cases the cause of death was not reported. Death due
mainly to diabetes was not observed so often as in the Cushing series, in
which 6 such fatalities and 7 due to cardiovascular changes were reported.

Among the 30 patients with acidophil adenoma who were followed up,
17 were found fully able to work (56.6 per cent), and 2 were alive without
any symptoms but did not report exactly about their ability. There was a
reduced ability in 7 cases (23.3 per cent), mainly because of fatigue and head-
aches (3), hypertension (2), and visual failure (2). Four patients were unable
to work (13.3 per cent), 3 of them because of progressing acromegaly, fatigue
and headaches and 1 on account of epileptic fits.

### TABLE 4

Survival Period of Patients with Acidophil Adenoma

<table>
<thead>
<tr>
<th>Elapsed Time after Operation</th>
<th>Maximum Number of Patients</th>
<th>Untraced</th>
<th>Alive</th>
<th>Per Cent Alive</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years</td>
<td>44</td>
<td>3</td>
<td>31</td>
<td>75.6</td>
<td>10</td>
</tr>
<tr>
<td>4 years</td>
<td>37</td>
<td>4</td>
<td>21</td>
<td>68.6</td>
<td>12</td>
</tr>
<tr>
<td>6 years</td>
<td>33</td>
<td>3</td>
<td>17</td>
<td>56.6</td>
<td>15</td>
</tr>
<tr>
<td>10 years</td>
<td>18</td>
<td>5</td>
<td>7</td>
<td>33.8</td>
<td>6</td>
</tr>
<tr>
<td>14 years</td>
<td>2</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

In contrast with the chromophobe adenoma cases, visual failure is rarely
the cause of postoperative inability in acromegalis. Usually there is a
marked variation in intensity of the acromegaly after operation; active and
inactive periods alternate, with intervals of shorter or longer length, and
sometimes with spontaneous remissions. The prolonged follow-up revealed
that acromegaly progressed without remission in all but 5 cases. In these 5
patients the symptoms did not advance; there was even a slight improve-
ment in 3 of them due to remission of the hypertrophic soft tissues, especially
on the face. Similar observations were made in fugitive acromegaly of pa-
tients with chromophobe adenoma, which frequently disappeared after re-
moving the tumor.

The periods of survival of acromegalic patients are recorded in Table 4.
These data are much less favorable than those of the chromophobe ade-
nomata, although the average age of acromegalis is lower and there are
fewer old individuals among them. A considerable percentage of the patients
died after an interval of 4 years or more after operation.

**RECURRENCES**

Thirteen patients (12 chromophobe and 1 acidophil) were operated upon
again for recurrence of symptoms; that represents 5.2 per cent of those
operated upon for chromophobe adenoma and 1.8 per cent of the acromegals. The total number of surgical interventions was 16, as one patient was operated upon three times for recurrence, and another twice. To this number of recurrences 5 other chromophobe and 4 acidophil adenomata can be added; in these cases recurrences were proved by evident clinical symptoms or by autopsy. It is hardly possible to give exact percentile rates with regard to recurrences of pituitary adenomata, because they can occur many years after the primary operation. However, reliable data can be obtained from that part of the series that has been followed up carefully and in which at least 5 years have elapsed since removal of the tumor. By such standards a rate of recurrence of 10–15 per cent has been estimated for the chromophobe adenomata and 20 per cent for the acidophil. The effect of prophylactic x-ray treatment could not be analyzed on account of the lack of untreated controls, postoperative radiation having been given in nearly all cases.

Out of Cushing’s 247 patients with chromophobe adenoma, 44 were operated upon again for recurrence and 70 others died from recurrences (together 46 per cent). In the acidophil adenoma group the rate of recurrence was 37 per cent. The far fewer recurrences in our series indicate the advantage of a transfrontal operation from the standpoint of recurrence.

The symptoms returned usually within a few years after the primary operation, but some exceptions were recorded. Careful analysis of 20 cases revealed that the first symptoms of recurrence appeared in 2 patients within 1 year, in 6 within 2 years, in 1 within 3 years, in 5 within 4 years, in 3 within 5 years, in 1 within 6 years, in 1 within 7 years, and in 1 within 8 years after the first operation. Consequently, in a vast majority of the cases the recurrence is to be expected within 5 years after operation. The first sign is mainly visual failure, in many cases a rather rapid loss of vision; it was observed in 90 per cent of recurrences. But other symptoms can cause suspicion, too, varying according to the pathway of extension. Hypothalamic symptoms (drowsiness, polydipsia, polyuria) were observed in 5 cases, headaches in 8, epileptic fits in 1, and mental disturbance in 1. Sexual functions that have remained or improved after the primary operation can be lost again; amenorrhea or impotence was recorded in 4 cases. In 3 patients the chief sign of recurrence was the progression of their cavernous sinus syndrome. In 1 of these, ptosis of the left eyelid had been noticed before the first operation, and it improved considerably after removing the adenoma. Eight years later examination revealed total ophthalmoplegia on the same side and palsy of the trochlear nerve. The recurrent tumor was enucleated and a marked improvement has been recorded.

There was no histological evidence of malignancy, change in chromatin structure, polymorphism or increased mitotic activity in the recurrent adenomata; the microscopic picture was that of the usual chromophobe adenoma. The structure of the recurrent neoplasm was usually completely identical with that of the first tumor. This is rather striking in those 2 patients whose adenomata revealed a marked tendency to grow and to return. One of them had recurrences and repeated radical enucleations 4, 6, and 8
years after the primary operation. Walnut- and hazelnut-sized tumors were removed each time. Microscopically there was no evidence of malignancy, but the abundant blood supply of the adenoma was striking on all occasions. The cells were in alveolar arrangement around the coherent network of capillaries. They had a large protoplasm of highly cylindrical shape, and secreted colloid in abundance, which was deposited in the stroma in form of hyaline masses. The other patient had recurrences 2 and 5 years after the first operation. Each time the adenoma showed a somewhat papillary structure, but no polymorphism was found. On the basis of this evidence there is no histological explanation regarding the potency of growth or tendency to return of these tumors.

The removal of recurrent adenomata usually is not more complicated than the primary operation, and the transfrontal approach can be repeated several times without increased risk. The mortality rate of secondary procedures was even less, only 6.2 per cent. The expectation of patients who have had reoperations is not bad, although the late results are less favorable than those of patients without recurrence, especially regarding vision. Late examinations revealed that none of these patients regained full visual acuity or complete visual fields; there was moderate visual failure in 5 and severe loss in the other 5. Three patients regained full ability to work following the repeated interventions, but the ability remained reduced in 5, was minimal in 1, while 1 was not capable of self-support. The time of survival was not less than of those without recurrences; one patient died 2 years and another 3 years after the secondary operation, but the others are alive after the repeated intervention—4 after 2 years, 3 after 6 years, 1 after 7 years, 1 after 9 years, and 1 after 10 years.

SUMMARY

During the period 1929 to 1947, 292 patients with verified pituitary adenoma were treated and 300 operations performed. The series included 232 chromophobe, 55 acidophil, 2 basophil, and 3 malignant adenomata. The postoperative mortality rate was 11.3 per cent for the chromophobe and 9.5 per cent for the acidophil adenomata. There was a striking difference, however, between the group of intrasellar tumors and the group with extrasellar extension, the first having a mortality rate of 6.4 per cent, and the second, 35.0 per cent.

Cases of adenoma with extension in the cavernous sinus, cave of Meckel, temporal lobe, hypothalamus, or third ventricle were included. Those in which there was extension in the cavernous sinus did not reveal a higher postoperative mortality rate than cases of the usual adenoma. There were more fatalities among patients with hypothalamic signs, and the late results of operation were not favorable.

The ophthalmic and endocrine symptoms and the effect of the removal of the pituitary adenomata thereon are discussed.

Two years after operation or later, 54.5 per cent of the surviving patients
with chromophobe adenoma were fully able to work; the ability was reduced in 27.2 per cent of the cases, and lost in 18.3 per cent. Among the acromegalic patients the late postoperative ability to work was complete in 56.6 per cent, reduced in 23.3 per cent, and lost in 18.3 per cent. The radical transfrontal removal of the adenomata and the postoperative x-ray treatment in this series were followed by long survival periods and relatively few recurrences.

There were 16 operations for recurrence of the adenoma. The mortality rate after secondary procedures was less than that after primary operations, and the time of survival was usually long. The late results, however, were less favorable in regard to ability to work. Recurrence rates of 10 to 15 per cent for the chromophobe and about 20 per cent for the acidophil cases are estimated.

REFERENCES