GLIOMAS OF THE NEUROHYPOPHYSIS
AND HYPOPHYSIAL STALK

A PRELIMINARY REPORT
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The correlation between acromegaly and eosinophilic hypophysial adenomas was already old news (Benda 1901) when Cushing discovered the correlation between the equally peculiar syndrome named after him and the basophilic cells of the hypophysis. Vigilant and unbiased observation has shown that the correlation between the first two is not entirely absolute, and even less absolute between the second two. Nevertheless both syndromes are still regarded as the manifestations of specific endocrine hyperfunction. It has been known since the report of Babinski in 1890 that adiposogenital dystrophy may be the result of a hypophysial tumor. This combination more often referred to as Fröhlich’s syndrome, is generally considered to be the result of diminished activity of the hypophysis, i.e., hypopituitarism. It has been a widespread opinion that one of the main causes of hypopituitary syndromes are chromophobic hypophysial adenomas, i.e., tumors formed of the chromophobic or chief cells of the pituitary gland proper. This doctrine was first advanced by Norman Dott and Percival Bailey, 4 in a lecture in 1924. These authors made a broad attack on the whole question of hypophysial adenomas, analyzing all the previous research and the extensive data from 162 cases of tumor, 107 chromophobic, from the Cushing clinic. During the quarter of a century since their report, the theory of the chromophobic adenomas and their particular topographic, histologic and clinical characteristics has been blindly accepted and few attempts have been made to check its veracity. The few control studies (Kraus, 8 Roussy and Oberling16) have been mainly confirmatory in nature. The general conception laid out by Dott and Bailey was so amazingly simple and schematic that it is not surprising that it won such immediate and general recognition.

Their theory was roughly as follows. There are three kinds of hypophysial tumors, all deriving from the pars anterior, the pituitary gland proper. One kind, which is rare, comes from the smallest cellular component of the adenohypophysis, the basophilic cells; these basophilic growths are always small, seldom grow beyond the sella and therefore cause no symptoms due to pressure on adjoining structures. Much more common are the eosinophilic growths, originating from the eosinophilic cells occurring in large numbers in the normal adenohypophysis. These not seldom grow up out of the sella, become suprasellar in other words, and exert pressure on neighbouring structures, particularly the optic chiasm. The most common of all, accounting for 80 to 90 per cent of the hypophysial tumors, are the
chromophobica adenomas coming from the largest cellular component of the anterior lobe, the chromophobic or chief cells. It is these tumors that far the most often break through the sellar diaphragm and spread out in the suprasellar space, resulting in pressure on the chiasm, optic nerves and tractus opticus and infundibulum, tuber cinereum and other structures.

This theory does not explain the numerous and practically important topographic and clinical peculiarities of the tumors which the Cushing school call chromophobic adenomas. Nor does it leave any room for tumors arising in the neurohypophysis. "Primary tumors of the posterior lobe are practically unknown," said McLean.11

I have now made a study of the tumorous tissue in 10 cases diagnosed as chromophobica hypophysial adenoma at the Neurologic Clinic in Stockholm. In 2 cases the study was made post mortem with the tumor and brain in situ (Figs. 1 and 2) and in the other 8 the tissue removed at operation was examined. This study has shown that the opinion that chromophobica hypophysial adenomas constitute the bulk of the suprasellar tumors connected with the hypophysis needs revision, to say the least. Not less than 8 of the 10 tumors were undisputably or almost certainly gliomas of the ependymal type (Figs. 1–8, 12), corresponding most closely to the ependymomas of the Cushing-Bailey classification.

These tumors were highly cellular. The cells were well individualized as a rule, mostly elongated and arranged in sinuous garland-shaped strands in some places and in other places in rounded groups or acini sometimes separated by thin, often vascular connective-tissue membranes. These ependy-
mal-like cells often tapered off at one end and supported themselves with their narrow ends against capillary or precapillary blood vessels, forming corona-like figures around them. Many places showed rosettes or pseudorosettes grouped around narrow cavities. Cilia were not uncommon. I was not able to discover undisputable blepharoplasts. Nor did I see any multinuclear cells or mitosis. There was no necrosis but most of the tumors contained cysts with “colloid” contents. The cysts developed in the same way as in certain gliomas and neurinomas, viz., through “hyaline degeneration” of the matrix or exoplasm and confluence of the degenerated products to form single or multiple cysts of various sizes. (Figs. 7 and 8).

The 2 autopsied cases (Figs. 1 and 2) are particularly instructive. In both instances the tumor was composed of a small intrasellar portion and a much larger suprasellar portion, the latter projecting up between the two temporal lobes, pushing them apart and replacing the 3rd cerebral ventricle. The suprasellar portion lay subarachnoidally and was coated outermost with a thin connective-tissue membrane, a pia mater. Under this membrane was a thin layer of tissue built up in the same manner as the central nervous system, with mostly glia cells and a maze of glia fibrils. In some places this layer sent regular septa a short way into the tumor mass. There is no doubt that the suprasellar portion of the tumor was composed of a strong, neoplastically thickened hypophysial stalk. There was no capsule on the intracerebral crown of the tumor, the neoplastic tissue there merging without a sharp line of demarcation with the surrounding brain tissue.

Six of the operatively removed specimens were undisputable or almost
undisputable ependymomas. One of the other 2 contained a highly cellular tissue which was perhaps of gliomatous nature. In the other case, it is impossible for me to identify the nature of the tissue; it was of loose structure, as if vacuolated, and I have no idea what it was.

What is particularly noteworthy is that in most of the cases in which the neoplasm was identified as an ependymoma, the clinical picture corresponded in every respect with the "hypopituitarism" considered to be distinctive of the so-called chromophobic adenomas (Fig. 11).

Let us assume for the moment that the majority of the suprasellarly growing non-eosinophilic tumors connected with the hypophysis or its stalk are really gliomas, mostly ependymomas, arising from the neurohypophysis or hypophysial stalk. We then have the explanation for a large number of the puzzling topographic and clinical features previously mentioned.

1) This assumption would explain why they grow up out of the sella turcica and spread out in the suprasellar region much more often than other hypophysial tumors. They have a preformed route of propagation, the hypophysial stalk. It may also be that the tumor sometimes starts in the stalk, grows first suprasellarly and afterward down into the sella turcica. For that matter, it could happen that the tumor never extends down into the sella, but remains entirely suprasellar. (This should also be possible in the case of real adenomas originating in the anterior lobe, for the pars tuberalis of the latter coats the hypophysial stalk.)

2) It would explain why they much more often than eosinophilic adenomas cause pressure on the optic chiasm and the region of the tuber cinereum, with resultant defects in the visual fields and other disorders.

3) It would explain why they much more often than the eosinophilic adenomas are accompanied by little or no roentgenologic enlargement of

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Fig. 5. Case 4. Ependyma-like, folded bands of closely packed cells. Vascular channels, pseudorosettes and cilia are visible. Iron-hematoxylin stain (×370).

Fig. 6. Case 7. Papilla formation with central vessels. Heidenhain's iron-hematoxylin stain (×515).
the sella turcica or other roentgenologic changes in this space. For one thing, it would explain why the “niche” projecting from the anterior part of the sella so common in the roentgen picture accompanying eosinophilic adenoma is lacking in these cases. If these tumors started in the pituitary gland proper, there is no reason why they, too, should not dig themselves a niche.

4) It would explain why the endocrine vegetative disorders accompanying these tumors are entirely, or at least mainly, privative, the result of hypopituitarism.

5) It would explain why this endocrine vegetative syndrome does not occur in every case. The latter circumstance was mentioned by Dott and Bailey⁴ and has been confirmed occasionally in the Neurologic Clinic. The obvious explanation for this irregularity is that the tumors vary as regards

![Image](image_url)

**Fig. 7.** Case 6. Abundant cyst formation. Hematoxylin-eosin stain (X110).

**Fig. 8.** Case 7. Cyst formation through “hyaline” or “colloidal” degeneration of the tissue. Heidenhain’s iron-hematoxylin stain (X200).

the direction in which they grow, the region they occupy and the size they acquire.

6) It would explain why these tumors are much less responsive to roentgen treatment than the eosinophilic variety. Mature gliomas are generally insensible to the roentgen ray.

7) It would explain the missing tumors from the neurohypophysis and hypophysial stalk. Here they are!

Ependymomas occur in different frequencies in different parts of the central nervous system. They account for only 2.7 per cent of the Cushing and Bailey⁵ series of cerebral gliomas but for as much as 46 per cent of the Kernohan et al.⁶ series of intramedullary spinal tumors. I have seen them several times in the cauda equina, where they probably start in the filum
Eight cases of ependymoma derived from the neurohypophysis or hypophysial stalk:

<table>
<thead>
<tr>
<th>Cases</th>
<th>Patient’s Age at Onset of Symptoms</th>
<th>Length of Illness</th>
<th>Hypopituitarism</th>
<th>Sellar Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (autopsy)</td>
<td>16</td>
<td>5 yrs.</td>
<td>+</td>
<td>Slight</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>10 yrs.</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>10 yrs.</td>
<td>+</td>
<td>Enlargement</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>2 (1½) yrs.</td>
<td>+</td>
<td>Slight (pressure)</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>2 yrs.</td>
<td>+</td>
<td>Slight enlargement</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>13 yrs.</td>
<td>+</td>
<td>Enlargement</td>
</tr>
<tr>
<td>7 (autopsy)</td>
<td>45</td>
<td>3 mos.</td>
<td>probably</td>
<td>Slight</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>6 yrs.</td>
<td>–</td>
<td>Considerable enlargement</td>
</tr>
</tbody>
</table>

Ependymomas also vary in nature. Distinction has been made between a “tubular” form with irregularly branched cavities lined with ependymal tissue and a “solid” form in which the cells are often arranged in corona formation around the vessels. There is also a cystic form. Kernohan thought that this was a neuro-epitheliomatous form but Bailey believed that the cysts were formed around blood vessels. My ependymomas were more of the “solid” type though they had numerous cysts. As seen, however, my opinion as to their manner of development does not agree with that of either Kernohan or Bailey.

Neural tumors starting in or involving the neurohypophysis are not entirely unknown. Nonne reported a case of glioma in the neurohypophysis accompanied by adiposogenital dystrophy, but unfortunately without further anatomic information. Casper described a glioblastoma widely extended over the base of the brain which had infiltrated the hypophysial stalk and destroyed the neurohypophysis. He also described a bean-sized,
entirely intrasellar ganglioneuroma (histologically diagnosed by Benda) which had destroyed the neurohypophysis. In both cases the adiposity was late in setting in and the anterior lobe appeared to be intact.

This being the case, are there any chromophobic adenomas? Yes, undoubtedly. Roussy and Oberling\(^{16}\) described small chromophobic adenomas situated in the hypophysis. Close\(^{9}\) reported the finding of 39 adenomas in a largely unselected series of 200 hypophyses. The majority of the tumors were found in persons over 45 years old and they were much more common in cases where benign or malignant tumors were present elsewhere in the body. However, these tumors did not resemble those of Dott and Bailey. Most of them remained small and stayed in the hypophysis; the normal acinous architecture of the organ was lost in the adenoma; only occasionally was the adenoma separated from the surrounding glandular tissue by a thin connective-tissue capsule; the stroma was poorly developed in the adenoma; the cells were smaller than the normal chromophobic variety and sometimes the tumor presented the picture of a pure “Kernhaufen.” Rare examples grew to larger dimensions up to twice the size of the hypophysis, and occasionally grew beyond the limits of the sella. Two of the 39 tumors were eosinophilic and both of these were tiny growths; the others were chromophobic.

It may be that Roussy and Oberling’s “type à petites cellules principales” represents the genuine chief cell adenoma. It is hard to say how Dott and Bailey’s “simple strumous” or “alveolar” types correspond to Roussy and Oberling’s types. The latter authors spoke also of a “type indéterminé.” Judging by their illustrations, their type “à cellules claires” is the one which best corresponds to my ependymomas. None of these authors said anything about topographic or clinical differences shown by the various “chromophobic” types.

Those who are curious whether neurogenic hypophysial tumors may start from anatomic variants or anomalies or embryonic remains may find the following of interest. Langer\(^{9}\) in 1892, Benda in 1932, Romeis\(^{15}\) in 1940, Kiyono in 1926 and Floderus\(^{5}\) in 1944 encountered cysts in the posterior lobe of an otherwise normal hypophysis which they believed to be remains of the infundibulum extending down in the neurohypophysis during the fetal stage, though the walls of these cysts were not lined with ependymal tissue. Judging by Langer’s figures, his growths were craniopharyngiomas. Sternberg\(^{17}\) reported having seen groups of large epithelial cells which he believed to be neuroepithelial elements in a hypophysial stalk and concluded it was a question of “choristoma.” Priesel,\(^{13}\) Kraus,\(^{8}\) Roussy and Oberling\(^{16}\)
and Romeis observed occasional examples of "Gewebsmissbildungen" or "ortsfremde" cells of essentially similar appearance. Floderus encountered the same formations and, like Sternberg, considered these palely staining, finely granulated cells with a large cytoplasm and small nucleus to be neuroepithelial and "characteristic." On the other hand, Löffler, who went so far as to speak of "Geschwülste im Hinterlappen und im Stiel," regarded the cells as immigrants from Rathke's pouch. Glandular ducts and follicles with ciliary epithelium often wander into the posterior lobe from the pars intermedia or the epithelium of the hypophysial cavity. They are generally considered, therefore, as belonging to the anterior lobe. The same is true, Rasmussen believed, of the isolated cysts lined with ciliary epithelium in the posterior lobe which Luschka described in 1860 and traced to the neural tube.

Haberfeld examined the hypophysis in 6 fetuses. In 5 cases the uppermost and lowermost sections of the posterior part of the neurohypophysis showed glia-cell groups containing cysts lined with ependyma-like cells, some ciliated, the basal parts of which disappeared in a maze of glia fibrils. Haberfeld discovered similar formations in 10 out of 12 newborn children and in 1 out of 3 children under 3 years old, but never in adults. Apparently, therefore, he had observed a type of fetal formation which disappears soon after birth. Haberfeld suspected that it might be the starting-point for neoplasms.

The "fetal" cellular groups in the anterior lobe described by Kraus are
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particularly worthy of note. The cells correspond in type to the early embryonic hypophysial cells which occasionally (Kraus, Roussy and Oberling) proliferate to form genuine adenomas in the anterior lobe. Seen in the pictures of Kraus, and Roussy and Oberling, these adenomas are highly reminiscent of ependymoma or papilloma, though their cells are more slender. Judging from experience hitherto, this form is very rare.

It is by no means established by the present series that all or even most of the tumors situated suprasellarly and connected with the hypophysis are ependymomas starting in the neurohypophysis or hypophysial stalk. A much more extensive analysis of a much larger series is required to settle this question. It may well be that other gliomas besides ependymomas arise in this region. The existence of genuine chromophobic hypophysial adenomas may be considered established. The only question is how big they grow and how often they occur. So much is certain, however, that this whole question must be taken up again and it may be that my assumption will prove to be correct. Several of the “chromophobic adenomas” reproduced in the articles by Dott and Bailey and Roussy and Oberling look to me more like ependymomas. The same is true of the drawing in Bailey’s book, and his description of the frequently elongated cells which “may seem to radiate around the vessels” in a scanty stroma is also suggestive of ependymoma.

Eosinophilic adenomas are of quite different nature, not only as regards staining properties. They are built up of irregularly sized, often multinuclear, generally rounded cells with irregularly sized nuclei, lying in disorderly

Figure 14. Real chromophe hypophysial adenoma, partially suprasellar. (A) Heidenhain’s iron-alum-hematoxylin stain, X170. (B) Ethyl-violet-orange stain, X225.
masses with no stroma, contain few vessels and have a marked tendency to necrosis.

A few words, finally, regarding topographic and clinical features. Bailey¹ said in 1948 that there was hardly any difference macroscopically between the two types of suprasellar tumors, viz., the chromophilic and chromophobic adenomas, to use the terminology of the Cushing school. The only exception, he said, was that the eosinophilic variety was generally smaller and grew more slowly, though it too could reach considerable size. But there was no consistent or general difference between them, in his opinion, as regards topography, as regards their direction of growth. Schaeffer (1924) has shown that the position of the chiasm in the anteroposterior direction varies greatly from person to person. My series contains cases of ependymoma the suprasellar portion of which grew so far anteriorly in relation to the chiasm as to cause blindness on one side, obviously due to pressure on the optic nerve, and temporal hemianopsia on the other. But I have also seen examples of eosinophilic adenoma with acromegaly that caused homonymous hemianopsia, in other words, that operated relatively far back in relation to the chiasm. In both the autopsied cases the suprasellar portion of the tumor lay posterior to the chiasm. On operation for suprasellar tumors it may be difficult to learn what the conditions are behind the chiasm, for the operation is generally done from the front.

As was first shown convincingly by Guthrie in 1913, Napoleon the Great suffered from severe progressive hypopituitarism. In 1932 Krogius succeeded in making the more precise diagnosis of hypophysial tumor. According to the Dott-Bailey scheme, Napoleon’s case would be a textbook example of chromophobic adenoma. For my part, I am inclined to suspect an ependymoma starting in the hypophysial stalk. Judging from the clear description in Talleyrand’s memoirs, Napoleon had his first observed epileptic fit in 1805, 16 years before he died. The intractable vomiting which beset him shortly before death may have been of cerebral origin. This disease must have contributed essentially to the downfall of the emperor.

REFERENCES