Regeneration of the human pituitary

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The pituitary remnant was examined in 13 patients in whom a stereotaxic, transsphenoidal, high-frequency coagulation had been performed because of widespread metastatic disease. The patients were divided in three groups according to the state of regeneration of pituitary tissue. The first group (patients dying 3 to 7 days after surgery) showed only signs of acute necrosis. The second group (patients dying 24 to 219 days after surgery) demonstrated mitotic figures and regenerated areas in the adenohypophysis. The third group (patients dying 252 to 353 days after surgery) showed no mitoses but large areas of regenerated glandular cells as a sign of completed regeneration. It seems that the pituitary can regenerate provided that the dominating hypothalamic centers remain undamaged during hypophysectomy.

KEY WORDS  ·  pituitary regeneration · hypophysectomy

Pathologists and neurosurgeons generally agree that the human adenohypophysis does not regenerate after partial destruction. Some discussion exists concerning the regenerative capacity of animal pituitaries. Some authors think that regeneration can occur, others deny this possibility, while a third group revised their opinion. Since it is known that a partial or complete return of pituitary function can take place after surgical or radiological destruction of the gland, it was supposed that the pharyngeal hypophysis, other extrahypophysial dystopic pituitary tissue, or the pars tuberalis might assume part of the function.

During the evaluation of the clinical results of stereotaxic, transsphenoidal electrocoagulation of the pituitary in cancer patients, we reviewed the microscopical slides of some patients who had died at various time intervals after the hypophysectomy. We then briefly mentioned definite signs of glandular regeneration on the preparations examined. This paper will present the details of our observations.

TABLE 1
Occurrence of signs of pituitary regeneration in 13 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Survival Time (days)</th>
<th>Mitoses*</th>
<th>Regenerated Pituitary Cells*</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
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<td>4</td>
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<td>8</td>
<td>70</td>
<td>76</td>
<td>+</td>
<td>+</td>
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<td>9</td>
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<td>81</td>
<td>+</td>
<td>+</td>
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<td>10</td>
<td>45</td>
<td>208</td>
<td>+</td>
<td>+</td>
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<td>11</td>
<td>48</td>
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<td>+</td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>252</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>66</td>
<td>353</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

* – = absent, + = moderate, ++ = remarkable.
Material and Methods

The histological sections of the remaining pituitary tissue of 13 patients (ages 36 to 77 years) dying from metastatic cancer (2 prostate, 11 breast) were examined. A stereotaxic transsphenoidal high-frequency electrocoagulation of the pituitary had been performed 3 to 353 days before death. The details concerning the operative technique and the clinical results have been published. At autopsy the entire sella was removed in nine cases, the pituitary alone in four. The specimens were fixed in 4% formalin, then decalcified if necessary, and embedded in paraffin. Frontal sections of the entire sella were obtained in five cases and sagittal sections in four. The sections were stained with hematoxylin and eosin.
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and PAS-orange G. Quantitative determinations were not possible since only an average of four sections without defined distances from each other were at our disposal. The available sections were distributed at random through the sella. All sections were examined with a light microscope using an oil immersion objective with a magnification of 100x and a numerical aperture of 1.30.

Results

The 13 patients can be easily classified into three groups according to the histological findings (Table I). The first group, consisting of the three patients who died 3 to 7 days after the surgical procedure, showed only signs of acute necrosis and no evidence of regenerative processes. There were large areas of destruction, some of which were of mechanical origin, with electrode tracts and small hemorrhages. Others showed evidence of electrical current cell destruction characterized by cell whorls, elongation of cells and nuclei, and eosinophilia of the cytoplasm (Fig. 1). Some parts usually situated in the lateral region of the sella had a more or less normal appearance with only occasional cell vacuolation. No mitoses or other signs of regeneration were seen.

The second group of patients died 24 to 219 days after operation and showed clear evidence of active regeneration. The center of the destroyed gland still contained the necrotic remnants of the coagulated pituitary with electrode tracts (Fig. 2 upper).

![Fig. 3. Case 7. Died 72 days after surgery. Upper Left: Metaphase in eosinophilic pituitary cell. H & E, X 2000. Upper Right: Area of regenerated basophilic cells containing various amounts of granules. The basophilic regenerated areas are always smaller than eosinophilic or chromophobe fields. H & E, X 700. Lower Right: Metastasis of mammary carcinoma demonstrating mitotic figure. Compare different cell structure with dividing pituitary cells (upper left photograph and in Fig. 4). No secretory granules are present. H & E, X 2000.](image-url)
The necrotic mass had only slowly been removed by macrophages and replaced by collagenous connective tissue. The viable pituitary remnants were usually situated in the lateral parts bordering the cavernous sinus and under the sellar diaphragm. These frequently contained mitotic figures (Figs. 3 upper left and 4) in eosinophilic and chromophobe cells and rarely in basophilic cells. They were particularly frequent in patients who died 29 and 76 days after surgery (Table 1). Some parts of the pituitary tissue showed the characteristics of the regeneration (Fig. 2 lower) commonly seen in the third group.

The third group, consisting of two patients who died 252 and 353 days after the electrocoagulation, showed no evidence of progressive regeneration; rather, the process seems to have been completed. Only regenerated areas were seen; these were of different sizes and some showed nodular features (Fig. 5 upper). They contained one predominant cell type (Fig. 2 lower left and 5 lower left). This uniformity differed entirely from the architecture of the normal pituitary in other regions of the gland (Fig. 5 lower right). The normal lobulated structure was replaced by a diffuse type of adenoma-like tissue. Areas of regenerated basophilic cells were much rarer than those of eosinophilic regeneration (Fig. 3 upper right). In these cases the central necrosis had been replaced by a collagenous scar.

Discrimination between regenerating pituitary and growing metastases was important since cancer cells often show mitoses (Fig. 3 lower right). A careful comparison of the cytoplasmic content never showed secretory granules in cancer cells. The variability of the nuclear structure and multiplicity of nucleoli in the surrounding cancer cells also helped in this distinction.

Discussion

Today's assumption that the human pituitary does not regenerate is generally derived from two different observations. First, no regeneration is seen after postpartum necrosis of the anterior pituitary, although a spontaneous improvement of the pituitary function after a new gravidity has been described. Second, no mitoses and regeneration could be observed after transfrontal sectioning of the stalk and curettage of the sella, or after the implantation of radioisotopes.

On the contrary, the observations of other authors, as well as our own findings, establish the regenerative capacity of the human adenohypophysis. In 1909 Erdheim and Stumme showed that the enlargement of the pituitary during pregnancy results from mitotic division of the pregnancy cells. The occurrence of mitotic figures in normal human pituitaries has been demonstrated by Romeis. Cameron is convinced that pituitary replacement can be complete if destruction is not too extensive. Connolly and Connell observed a patient who, 5 months after transfrontal stalk section and incomplete curettage of the sella, showed a regeneration of the stalk as well as most of the pituitary. Matheis and Dollmann described a microadenoma and four cases with adenomatous cell hyperplasia to 226 days after implantation of radioactive gold in 12 patients; they thought that these changes had existed before the radioactive implantation.

Hardy reported a patient who underwent hypophysectomy because of severe, uncontrollable pain from progressive metastatic bone lesions. He was free of pain immediately after transnasal hypophysectomy. Six
months later, pain recurred, and endocrine-
logical studies showed reappearance of
gonadotropin and thyreotropin function.
Reexploration demonstrated a small piece of
anterior pituitary tissue, which was success-
fully removed. This operation rendered the
patient free of pain again.

Regeneration of the vascular channels of
the stalk is known to occur in animals and
in man. Our own findings demonstrate
the regenerative process (mitoses) as well
as the regeneration product after high-
frequency lesions of the adenohypophysis.
Mitoses are extremely rare in the normal

Fig. 5. Case 12. Died 252 days after surgery. Upper: Large nodular regenerated area protruding into fibrous scar. H & E, X 40. Lower Left: Detail of regenerated area showing adenoma-like architecture of a pure eosinophilic cell population. H & E, X 450. Lower Right: Area adjacent to regenerated field demonstrating usual lobular structure of the tissue containing eosinophilic, basophilic, and chromophobe cells. The pituitary tissue in this area is normal. H & E, X 450.
human pituitary. Their existence had been repeatedly questioned until Romeis24 proved their rare occurrence beyond any doubt. The appreciable number of mitoses that can be observed in the pituitary remainders described in our Group 2 proves increased cell proliferation.

There remains the question concerning the observation of the failure of pituitary regeneration in postpartum pituitary necrosis. Sheldon and Hertig28 and Russell25 described various patients who showed, besides acute thrombosis of the pituitary sinusoids with necrosis of the surrounding tissue, microinfarcts in the proximal stalk and the tuber cinereum. Four cases of Sloper and Adams80 demonstrated, in the acute phase after section of the stalk, hemorrhagic infarcts extending from the stalk into the median eminence. Macrophages loaded with hemosiderin could be found in the median eminence of chronic cases thus suggesting that an infarct had occurred.

We conclude that pituitary regeneration is only possible if the superimposed hypothalamic centers are functioning. This was definitely so in our pure pituitary lesions. In postpartum pituitary necrosis as well as after transfrontal stalk sectioning with or without curettage of the sella, additional lesions in the proximal stalk and the median eminence may explain the lack of regeneration. The hypophysiotropic hormones of the hypothalamus probably not only cause pituitary hormone release but also stimulate hormone synthesis10 and pituitary growth.

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References

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