HYPOPHYSECTOMY IN DISSEMINATED CANCER OF THE BREAST

By

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It is well known that castration as well as the administration of oestrogens or androgens may temporarily arrest the growth of malignant inoperable tumours of the breast.

Hence hypophysectomy was suggested for the treatment of this condition, when corticotrophin and cortisone became available for substitution therapy. Olivecrona and Luft, who were pioneers of this treatment, reported their first results as early as 1952 (Luft et al.). The first reports were promising, and hypophysectomy was therefore tried in most countries for the treatment of advanced cancer of the breast.

RATIONALE

The use of hypophysectomy in the treatment of breast cancer is based on the finding that 70–80% of tumours arising in mammary tissue are susceptible to hormonal fluctuations like the tissue from which they originated.

Careful studies on the effect of hormones on the mammary tissue of the rat have been reported by Cowie & Folley (1955). They found complete atrophy of the mammary tissue following castration and hypophysectomy. Administration of ovarian hormones to the operated rats, however, could not arrest the progressive atrophy of the mammary cells, even in very high doses. Administration of prolactin did arrest the atrophy, but the cells did not regenerate. On the other hand, when prolactin and oestrogens were administered at the same

1. This study was made with aid from the Danish National Anti-Cancer League.
time, rapid growth of the mammary cells was induced. The latter experiments also showed that this effect was obtained by surprisingly low doses of oestrogens. Treatment of the castrated, hypophysectomized rats with prolactin and oestrogens followed by administration of growth hormone and cortisone not only produced a rapid growth of the mammary cells, but also induced lactation. In other words, in the absence of prolactin growth of mammary tissue in castrated and hypophysectomized animals cannot be induced.

**INDICATION FOR HYPOPHYSECTOMY**

Since the preliminary reports demonstrated the inhibitory effect of hypophysectomy on mammary tumours, there has been a good deal of discussion among the various scientific groups as to the most favourable time for operation.

The extreme views are (1) Hypophysectomy should be a prophylactic measure, performed simultaneously with the operation of the primary tumour, i.e. before the appearance of possible metastases. (2) Hypophysectomy should not be carried out until all other kinds of treatment have proved ineffective. In the present study, the latter alternative was chosen, as psychologically it seemed desirable to defer the operation as long as possible and also because by performing the operation at such an advanced stage, there was a possibility of assessing the effects of hypophysectomy without having to consider other factors. In such circumstances it would be extremely difficult to obtain a control material, but any remission induced at a stage at which all hope was abandoned, could only be ascribed to the actual hypophysectomy.

**RESULTS**

Collaboration between the Radium Centre, Copenhagen and the Neurosurgical Department of the University Hospital resulted in the hypophysectomy of 50 patients suffering from breast cancer with widespread metastases. As already mentioned, these patients were not hypophysectomized until treatment, such as operation, X-ray therapy, and hormone therapy had been abandoned. Before being subjected to the operation, the patients were made acquainted with the implications of the intervention and the side effects they might expect.

The age of the patients ranged from 34 to 72 years, and their disease was of from 1 to 6 years' duration. All had diffuse metastases to bones and soft tissues. All were in great pain and were taking large doses of analgesics. Table 1 gives the distribution of metastases in the 50 cases.

All the patients were treated according to the following schedule: Immediately before operation they received 200 mg. cortisone i. m. and after the operation 200 mg. cortisone i. m. In the operation theatre the patients were given 100 mg.
hydrocortisone dissolved in half a litre of glucose solution as an intravenous drip. On the first postoperative day they had 150 mg. cortisone twice, on the second day 100 mg. twice, on the third day 75 mg. twice, on the fourth day 50 mg. twice and on the fifth day 25 mg. twice. The last dose was given in tablet form. The medication was continued by the administration of 25 mg. cortisone twice daily and 100 units of thyroid extract daily.

On this regimen the postoperative course was smooth in the great majority of cases. Even so, all the patients were carefully supervised every hour. During the first few days 6 patients exhibited signs of incipient adrenal cortical insufficiency, as manifested by a rise in temperature followed in a few hours by falling blood pressure and rising pulse rate. These signs, however, rapidly yielded to intravenous hydrocortisone.

A postoperative increase in the urinary output was a constant finding. The explanation is that in addition to the anterior lobe, the posterior lobe of the hypophysis had also been removed. Within about 5 days, the urinary output increased to about 5–7 litres a day, continued at this level a few months and then decreased in most cases to 2–4 litres daily. Actual diabetes insipidus did not develop in any of the cases presumably because the neurosecretory cells in the supraoptic and paraventricular nuclei were not affected by the operation. It must be assumed that these patients have a constant secretion of the antidiuretic hormone without any form of regulation. If the urinary output remains high after the course of a few months, it is worthwhile trying to reduce the dose of cortisone slightly. This will reduce the output of urine, as a direct antagonism exists between cortisone and the antidiuretic hormone.

Hypophysectomy produced remission in 21 out of the 50 patients who were operated on, as already mentioned, after all other kinds of treatment had proved ineffective.

Remission, in the present study, is taken to mean subjective and objective improvement, i.e. relief of pain and normalization of the temperature and blood. Metastases remain stationary or regress (Table 2).

The duration of the remission in the 21 patients was relatively short, but this

\[
\begin{array}{|c|c|}
\hline
\text{Predominantly skeletal metastases} & 28 \\
\text{Predominantly local metastases} & 3 \\
\text{Predominantly pleural and pulmonary metastases} & 10 \\
\text{Hepatic metastases} & 5 \\
\text{Cerebral metastases} & 4 \\
\hline
\end{array}
\]
Table 2.
Effect of hypophysectomy in 50 patients suffering from breast cancer with widespread metastases.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>21</td>
</tr>
<tr>
<td>Relief of pain</td>
<td>28</td>
</tr>
<tr>
<td>No improvement</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 3.
Duration of remission following hypophysectomy in 21 patients with cancer of the breast.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 months in 5 patients</td>
<td>2</td>
</tr>
<tr>
<td>3–6 months in 3 patients</td>
<td>1</td>
</tr>
<tr>
<td>6–12 months in 6 patients</td>
<td>5</td>
</tr>
<tr>
<td>12–16 months in 7 patients</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 4.
Effect of hypophysectomy on metastases in 21 patients who obtained remission.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression of metastases</td>
<td>5</td>
</tr>
<tr>
<td>Unchanged metastases</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 5.
Relation between menstruation and effect of hypophysectomy.

<table>
<thead>
<tr>
<th>Menstrual Status</th>
<th>Number</th>
<th>Remission</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal and menopausal</td>
<td>12</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5–10 years after menopause</td>
<td>14</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>More than 10 years after menopause</td>
<td>15</td>
<td>3</td>
<td>12</td>
</tr>
</tbody>
</table>

must take into account the very advanced stage at which the operation was performed. The average period of remission was about 8 months (Table 3).

Out of the 21 cases with remission, the metastases remained unchanged in 16, whereas they regressed in 5 (Table 4).

In considering the susceptibility of mammary tumours to hormones, there is
Table 6.
Complications in 50 patients following hypophysectomy.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blindness in R. eye</td>
<td>6</td>
</tr>
<tr>
<td>Anosmia</td>
<td>17</td>
</tr>
<tr>
<td>Died within 4 weeks</td>
<td>11</td>
</tr>
<tr>
<td>(including 9 with hepatic and cerebral metastases)</td>
<td></td>
</tr>
</tbody>
</table>

little doubt that tumours which arise around the menopause are more susceptible than tumours which arise later in life. This is also in agreement with the finding in the present series. Thus if the relation between menstruation and effect of hypophysectomy is studied, it will be seen that the best effect is obtained at the time of the menopause, and that this deteriorates with the length of the interval after the menopause (Table 5).

The hypophysectomy was well tolerated. Only 3 patients died within the first two weeks.

The first patient who died after the operation was a 55-year-old woman with widespread hepatic and cerebral metastases. On the fifth postoperative day she developed bilateral parotitis and pneumonia, and despite intensive treatment could not overcome the infection. The second patient was a 40-year-old woman with local and skeletal metastases, who developed pneumonia and succumbed despite massive antibiotic therapy. The third fatal case was a 55-year-old woman with hepatic and pulmonary metastases who died in a state of generalized carcinosis. Within the first four weeks 11 patients died; 9 of these had hepatic and cerebral metastases. In 6 cases, moreover, the optic nerve had to be cut because of technical difficulties in the course of the operation. Seventeen patients stated that they had lost the sense of smell after the operation (Table 6).

**DISCUSSION AND CONCLUSION**

As mentioned above, the remission obtained in about half the operated cases was relatively brief, though it must be borne in mind that the material was not selected and that all the patients were operated on at a very advanced stage. The series also includes patients with metastases to the brain and liver and such patients will not be subjected to this operation in the future.

In evaluating the results, it is essential to be certain that the hypophysectomy has been complete. Out of the present series, the hypophysectomy proved to have been incomplete in 12 (autopsy findings).

Hypophysectomy is not, as one might believe, particularly incapacitating; it does not prevent the patient from leading a normal life, if substitution therapy
is carefully carried out. Mentally, the patients are entirely normal, as long as they are receiving the correct dose of thyroid; otherwise they may be somewhat torpid and dull. They are pale, with an almost milky white skin due to decreasing pigmentation. The electrolyte balance is not affected, so there is no need to administer mineralo-corticoids. It has been demonstrated by Farrell (1956) that about 66% of the aldosterone production of the adrenal cortex continues after hypophysectomy. Luetscher (1956), studying the aldosterone excretion in the urine of hypophysectomized patients, found that it was at the lower limit of normal. When the salt intake was restricted, it might increase up to 7 times the initial value. Thus, it may be said that even under unfavourable conditions, hypophysectomized patients are able to maintain their electrolyte balance.

The fasting blood sugar is 10–20% lower in hypophysectomized than in normal subjects. The explanation is partly reduced gluconeogenesis in the liver and partly increased uptake of glucose from the blood. The latter in turn is due to the deprivation by hypophysectomy, of the greater insulin inhibitory factor. Some inhibition is present, however, as the patients are constantly treated with cortisone.

If hypophysectomized patients are exposed to infections or if they have to submit to any further major operations, the daily dose of cortisone has to be increased by 50–100% as in all other patients on cortisone medication.

If any conclusion can be drawn from the present studies, it may be said that hypophysectomy is a treatment which may be used in otherwise hopeles cases of breast cancer with widespread metastases. In such cases it can produce a remission of varying duration. Furthermore, it may be said that in some of the cases that do not obtain remission, there may be subjective improvement, relief of pain, and a considerably decreased consumption of analgesics. In other words, hypophysectomy may be considered an advance in the treatment of late stages of breast cancer.

**SUMMARY**

Hypophysectomy was performed on 50 patients with disseminated cancer of the breast. Twenty-one obtained remission, viz. subjective and objective improvement. Twenty-eight were relieved of pain. The average duration of the remission was about 8 months. The most favourable effects of hypophysectomy were obtained in menopausal patients. Patients with metastases to the liver and brain did not respond. It is concluded that hypophysectomy marks an advance in the treatment of late stages of breast cancer.
REFERENCES


