ENDOCRINE TREATMENT
OF METASTATIC CANCER OF THE BREAST
AND PROSTATE

By

Rolf Luft, Herbert Olivecrona and Denis Ikkos

The possibility of a relation between endocrine status and cancer has been recognised since long. In 1836 Cooper wrote that the symptoms of women with breast cancer were «augmented by the approach of menstruation and decline as the period is passing». Moreover, he recorded the fact that exacerbations of the disease occur at menopause. Recent metabolic studies (Pearson et al., 1954) confirmed the opinion of Cooper: it was found that in females with «estrogen dependent» breast cancer, the urinary calcium excretion is cyclic and parallel to the menstrual cycle. Schinzinger in 1889 suggested oophorectomy in metastatic breast cancer. Beatson in 1896 reported remissions in inoperable breast cancer after bilateral oophorectomy, thus offering the first clear-cut observation on the relation of hormonal environment and cancer. In 1905 Lett in a series of 99 cases confirmed the results of Beatson: he found that the percentage of remissions in premenopausal women (75 cases) amounted to 41.3 per cent.

The work of Loeb (1919) offered the first systematic experimental study on the relation between malignant tumors and hormones. The experimental approach received a new impetus from the work of Lacassagne who, in 1932, demonstrated the carcinogenic properties of estrogens.

These pioneering observations have been followed by a large body of clinical and experimental work on the relation between hormones and cancer. The problem is of large interest both for theoretical and practical reasons. The regression of cancer in some cases by endocrine treatment demonstrates that cancer is not always autonomous, i.e. independent of normal physiological

1) Based on an address at the Second Acta Endocrinologica Congress in Oslo, August 15, 1956.

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mechanisms governing cell growth and development. The practical importance of the problem in breast and prostatic cancer is illustrated by the following: of the patients appearing for initial treatment, 30 per cent of women with breast cancer and 90 per cent of men with prostatic cancer are inoperable. Of the women submitted to radical mastectomy 50 per cent may have recurrences at the end of five years (Marshall & Whitmore, 1958, Treves, 1954). Thus, about 90 per cent of cases of prostatic carcinoma and 75 per cent of cases of breast carcinoma will at some time require therapy other than radical surgery. In many of these cases endocrine treatment offers worthwhile palliation of the diseases and prolongation of life, many times an active one, although cure of cancer by hormonal treatment has not been achieved.

It is not the purpose of the authors to review the extensive literature on the relation between hormones and malignant growth, since excellent extensive reviews are available. Therefore the present status of the endocrine treatment of malignant diseases will be reviewed in short with special emphasis on actual questions. Since the practical results in malignancies other than breast and prostatic cancer in man (cancer of the uterus and thyroid, lymphomas) are limited, only these two types of malignancies shall be dealt with in the present paper.

_Cancer of the female breast_

The usual forms of endocrine treatment in cancer of the female breast are as follows:

A) _Hormone administration:_
   1) testosterone propionate (50–100 mg., 3 times a week) all ages
   2) estrogens (Stilbestrol 10–15 mg./day) postmenopausal

B) _Ablative procedures:_
   1) castration premenopausal
   2) adrenalectomy castrated + postmenopausal
   3) castration + adrenalectomy all ages
   4) hypophysectomy all ages

Combinations of different forms of treatment have been used, such as testosterone + estrogens, castration + testosterone and so on. Moreover, when one hormonal treatment becomes or is ineffective another one is tried, sometimes with favorable effect.

Representative results obtained by these different procedures are given in Table 1. In this connection, the authors want to mention that big difficulties were encountered in the selection of these data. In many of the studies published, either the exact criteria on which percentage responses were based
Table 1.
Results of endocrine treatment in metastatic cancer of the female breast.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Status</th>
<th>Number of cases</th>
<th>Objective remissions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>/o</td>
<td>Mean duration months</td>
</tr>
<tr>
<td>Androgen</td>
<td>premenopausal</td>
<td>54</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>postmenopausal</td>
<td>113</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>postmenopausal</td>
<td>76</td>
<td>32</td>
<td>13.5</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>premenopausal</td>
<td>75</td>
<td>44</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>—o—</td>
<td>131</td>
<td>44(2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>postmenopausal</td>
<td>46</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>all ages</td>
<td>3353)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oophorectomy + all ages</td>
<td>95</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>—o—</td>
<td>345</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Hypophysectomy</td>
<td>all ages</td>
<td>41</td>
<td>54</td>
<td>14 + (6)4)</td>
</tr>
<tr>
<td></td>
<td>—o—</td>
<td>(27)3)</td>
<td>(52)</td>
<td>(16.5 + (1)4)</td>
</tr>
<tr>
<td></td>
<td>—o—</td>
<td>67</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>—o—</td>
<td>194</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

1) Soft tissue metastases (excluding primary tumor).
2) Bone metastases.
3) X-ray castration in all but 15 cases.
4) Number of patients still in remission at the time of evaluation.
5) Cases with effective observation time more than two years.

are not given, and/or the duration of the remission is not presented. Moreover, many times it is not clear whether objective or only subjective amelioration was taken as remission. Subjective amelioration is certainly a worthwhile palliation in cancer cases. However, it might not be an appropriate basis for
the comparison of the results obtained with different endocrine treatments of malignancies. This is of special importance in studies with testosterone. It is well known that with such a treatment there is a large discrepancy between the subjective and objective responses of the patients. Thus, marked subjective amelioration has been observed in cases, in which objective evidence demonstrated continuation of the cancer growth (Nathanson, 1952). These facts illustrate the need for a standardization of the criteria used to evaluate the response of cancer to endocrine treatment and of the report of the results.

The data in Table 1 are taken from studies, in which objective criteria were used for the evaluation of the results. Only the percentage of responses and the mean duration of the remission are given. The mean survival time of cases who responded to a given treatment is sometimes compared with that of the patients who did not benefit from the treatment. The difference in response might, however, be connected with differences in the type of cancer and/or the status of the patients at the initiation of the treatment. Consequently, comparison of the survival time on this basis may be misleading and, therefore, such data are not given in Table 1.

The following points from Table 1 are of special interest:
1) by ablative treatment a higher percentage of remissions is obtained than by hormone administration;
2) approximately 50 per cent of the patients with metastatic breast cancer are benefited by ablative endocrine treatment; this demonstrates that in half of the cases the cancer growth is hormone-dependent at the stage of initiation of the treatment;
3) endocrine treatment is not curative for breast cancer as demonstrated from the limited duration of the remission;
4) remissions of soft tissue lesions were induced by estrogens in about one fourth of premenopausal cases;
5) oophorectomy induced remissions in 11 per cent of the postmenopausal patients.

The percentage of remission after X-ray castration is lower than that after surgical castration. This may, however, be due to incomplete castration by the usually employed technique.

Cancer of the male breast

This form of cancer is unusual in comparison to the cancer of the female breast, and the data available on the effect of endocrine treatment (Table 2) are, consequently, very limited. From the data in Table 2 it seems that, as for female cases, a larger percentage of remissions is observed after ablative endocrine treatment than after hormone administration. Moreover, it seems probable that, by such procedures, remissions are induced in a larger percentage of male than female patients with breast cancer.
Table 2.
Results of endocrine treatment in metastatic cancer of the male breast.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of cases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>treated</td>
<td>remissions</td>
</tr>
<tr>
<td>Estrogen</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Castration</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hypophysectomy</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Cancer of the prostate

The usual forms of treatment in prostatic cancer are:

A) **Hormone administration:**
   1) estrogens (Stilbestrol 5–15 mg./day).

B) **Ablative procedures:**
   1) castration
   2) adrenalectomy
   3) hypophysectomy.

Adrenalectomy and hypophysectomy have so far been tried in a limited number of cases. In the evaluation of the results of the endocrine treatment of metastatic cancer of the prostate, difficulties similar to those for cancer of the female breast were encountered. The data in Table 3 were selected on the basis of the same criteria as those in Table 1. The general opinion seems to be that treatment by estrogens and/or castration induces objective remissions in about 75 per cent of the cases, and that the mean duration of the remissions is approximately 11 months. The limited experience with adrenalectomy is so far not encouraging. This procedure induced remissions only in about 10 per cent of the cases operated on. This percentage is much smaller than that obtained by this procedure in metastatic cancer of the female breast (45%o). The limited experience with hypophysectomy seems encouraging. In half of the patients who had previously been treated by estrogens and/or castration, this operation induced new remissions lasting from two to more than 24 months.
Table 3.
Results of endocrine treatment in metastatic cancer of the prostate.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of cases treated</th>
<th>Duration of objective remissions months</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen, castration</td>
<td>0</td>
<td>75% / 11</td>
<td>Marshall &amp; Whitmore, 1953</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>30% / 3</td>
<td>Nesbit &amp; Baum, 1950</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>+</td>
<td>46 / 4</td>
<td>see Morales et al., 1955</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>5 / 0</td>
<td>--o--</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>17 / 2</td>
<td>Randall, 1954</td>
</tr>
<tr>
<td>Hypophysectomy</td>
<td>+</td>
<td>7 / 5</td>
<td>Luft et al., 1956</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>4 / 1</td>
<td>Pearson et al., 1956</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>4 / 2</td>
<td>Scott, 1954</td>
</tr>
</tbody>
</table>

DISCUSSION

The remission obtained by endocrine treatment in hormone-dependent cancers of the breast and prostate are generally attributed to specific – and by some authors to unspecific – changes of the hormonal environment induced by the different therapeutic procedures.

A) Specific

1) Sex hormone control

   a) castration
   b) adrenalectomy
   c) sex hormone of the opposite sex (?)

2) Hypophyseal hormone(s) control (?)

   a) estrogen in women
   b) sex hormone of the opposite sex (?)

3) Sex hormone and hypophyseal hormone(s) control

   a) hypophysectomy
   b) sex hormone of the opposite sex (?)
   c) oophorectomy + adrenalectomy (?)

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B) Unspecific

1) unspecific change of the hormonal milieu,
2) anabolic effect of androgens and osteoblast-stimulating effect of estrogens.

The term sex hormones control is used to describe the elimination of the endogeneous secretion of sex hormones and/or neutralization of their biological effect on specific tissues such as breast and prostate. In analogy, the term hypophysal hormone control describes the elimination of pituitary hormone or hormones which are or can be connected with the growth and development of the normal, and probably cancerous, breast and prostate.

The first method used for sex hormone control, castration, induces remissions in a high percentage of patients. However, the sex hormone control achieved by this method is not complete. Shortly after castration the values for urinary estrogens or androgens are usually lower than the preoperative ones but then increase progressively reaching in some cases the preoperative levels (Satterthwaite et al., 1941, Scott & Vermeulen, 1942, Birke et al., 1954, 1955, Huggins & Dao, 1954, Dao & Huggins, 1955, Bulbrook & Greenwood, 1956).

Since the most probable source of sex hormone after castration is the adrenals, bilateral adrenalectomy has been employed for further sex hormone control (Huggins & Scott, 1945, Huggins & Bergenstal, 1952). In approximately half of the patients with cancer of the breast who were previously benefited from castration, new remissions were induced by adrenalectomy (Dao & Huggins, 1955, Pearson, 1956 a). Remissions were also observed in a few patients with cancer of the prostate who had been castrated previously (Huggins & Dao, 1953, Harrison et al., 1953, Randall, 1954). Therefore combined castration and adrenalectomy has been employed for a complete sex hormone control.

However, it is debated whether this double operation offers a complete elimination of estrogens and androgens from the body. It has been reported that sex hormone metabolites are found in the urine of castrated-adrenalectomized patients, although in amounts much smaller than preoperatively (Laidlaw et al., 1952, Munson et al., 1953, Bergenstal, 1956, Bulbrook & Greenwood, 1956). Other authors do not agree, however, with this view (Huggins & Scott, 1945, Birke et al., 1954, 1955). As a possible source for these sex hormones aberrant adrenal tissue, which is present in 30 per cent of humans (Graham, 1953, Falls, 1955) has been discussed. But can this aberrant tissue function when the patients are receiving 50–100 mg. of cortisone per day? It is also discussed whether these sex hormones might be derived from the cortisone used for substitution. This has not been proved. In this connection it is worth mentioning that in oophorectomized-adrenalectomized women androgens are converted to estrogens (West et al., 1956).

The use of the sex hormone control principle in the treatment of hormone-
dependent cancer of the breast and prostate is based on the principle that the growth of such tumors depends on the presence of estrogens and androgens. i.e. hormones which are connected with the growth of the normal cells of these organs. Experimental and clinical evidence generally support such a view. There are, however, observations which cannot be explained on the basis of this principle and suggest that other hormones, as well, are connected with malignant growth in man. For example, administration of homologous sex hormones in breast and prostatic cancer induce exacerbations but in a percentage which is smaller than that for the remissions after sex hormone control. In males with prostatic cancer exacerbation by androgens has been induced only rarely (Whitmore et al., 1954).

Moreover, even homologous sex hormones can induce remissions. Thus, estrogen in premenopausal women made soft tissue lesions regress in 22 per cent of the patients (Table 1). Large doses of estrogen (1000 mg. stilbestrol daily) in premenopausal women with breast cancer have only rarely induced exacerbations. In fact, regression of the tumor has been observed by such a treatment in some cases (Kennedy et al., 1955).

Castration induces remissions although sex hormone control is not complete. Further sex hormone control by adrenalectomy in breast and prostatic cancer does not induce remissions in all cases, which, according to the effect of previous castration, should be classified as estrogen or androgen-dependent cancer cases. This last observation might, on the other hand, result from a change of the tumor from hormone-dependent to autonomous.

Observations as the ones mentioned above can be explained only on the basis that, except for sex hormones, other hormonal factors are involved in the maintenance of the growth of cancer of the breast and prostate. There is increasing evidence that these other hormonal factors are the hypophyseal hormones.

Complete growth and development of the normal breast is under the control of the synergistic action of ovarian and directly acting pituitary, or pituitary-like placental hormones. Estrogen and/or progesterone did not prevent regression of the mammary glands in hypophysectomized-gonadectomized, and in some instances also adrenalectomized and thyroidectomized immature male rats. In similarly operated animals, duct growth was induced in the absence of ovarian hormones by combined treatment with growth and lactogenic hormones. Lactation, on the other hand, was induced only by combined treatment with ovarian (estrogen, progesterone) and hypophysial (growth, lactogenic) hormones (Lyons et al., 1955, Chen et al., 1955). In contrast, the experiment of Grayhack et al. (1955) did not prove any effect of prolactin on the restoration of prostatic weight by testosterone in castrated-hypophysectomized rats.

Although these experimental findings cannot be directly extrapolated to the growth of normal and/or cancer cells of breast in man, there are data which
suggest that pituitary hormones are of importance in women at menopause. Lactation of cancerous breast has been encountered, although rarely. Prolactin injection induced milk formation in two of five cases of breast cancer (Huggins & Dao, 1954). Administration of purified growth hormone induced subjective and metabolic exacerbation in a patient with breast cancer who was in remission after hypophysectomy. This exacerbation disappeared after discontinuation of the experimental treatment (Pearson et al., 1956). Kennedy et al. (1955) reported subjective and metabolic exacerbation of the disease in two cases of cancer of the prostate during growth hormone administration.

It is well known that administration of sex hormones, and especially estrogens, interferes with the normal function of the anterior pituitary. Moreover, it seems that this interference is not limited to the gonadotrophins. The amelioration of acromegalic patients by estrogens is considered as resulting from a decrease in the secretion of growth hormone. The beneficial effect of estrogen treatment in women with breast cancer can, thus, be explained as mediated through the pituitary hormones. Such a mechanism could also in part or whole explain the remissions induced in breast or prostatic cancer by sex hormones of the opposite sex. although the possibility that the effects of such treatment results from sex hormone control cannot be excluded.

It is also worth mentioning the well known fact that ablation of the gonads and/or adrenals influences the function of the anterior lobe of the hypophysis. The effects on hormones others than gonadotrophins and ACTH have not been studied. The possibility that remissions of breast or prostatic cancer, through castration and/or adrenalectomy, might be partially depending on pituitary factors remains to be investigated.

Further support to the view that pituitary factors are of importance in growth of breast cancer, is provided by the results achieved by hypophysectomy. Ex- tirpation of the hypophysis induced remissions in previously oophorectomized-adrenalectomized patients (Pearson et al., 1956). It has been questioned whether these results depend on atrophy of aberrant steroid-producing tissue (Pearson et al., 1956). But such a view seems rather improbable, as mentioned above.

On the basis of the available evidence it can tentatively be concluded that hormone-dependent cancer tissue of breast and prostate depends for its growth on the same hormonal factors as normal tissue of these organs. i.e. on sex hormones and hypophyseal hormones.

A complete hypophysectomy will, most probably, offer a complete sex and hypophyseal hormone control and, therefore, hypophysectomy may be advantageous in comparison with other endocrine treatment. If cortisol can be converted to estrogens or androgens, the sex hormone control would not be complete. But are sex hormones of any significance for cancer growth in man when hypophyseal hormones are absent? And in the case of a positive answer to this, which are the critical values? Another question in connection with
hypophysectomy is also of importance: can a complete hypophysectomy be achieved by destruction of the pituitary in the sella turcica only? Pituitary tissue is found outside the sella turcica, and it has been discussed whether this tissue may take over pituitary function after destruction of the hypophysis (Melchionna & Moore, 1938, Tönnis et al., 1954). But such a possibility seems rather improbable, since this extracelluar pituitary tissue is not connected with the hypothalamic area by nervous and direct humorous connections.

Finally, it should be mentioned that, according to some authors, the remissions after endocrine treatment result from unspecific changes of the endocrine treatment. But such a view is difficult either to prove or disprove.

From a practical point of view two questions are of importance:

1. which cases should be subjected to endocrine treatment?
2. which is the appropriate endocrine treatment in metastatic breast and prostatic cancer, and which sequence of methods should be followed?

When the treatment included only castration or hormone administration the selection of cases was of no special importance, since such treatment is usually devoid of serious consequences for the patient and, when appropriate, can be tried in every case. The question of selection of cases became of importance, however, when adrenalectomy and hypophysectomy were included in our therapeutic arsenal.

Different criteria of selection are being investigated. It has been suggested that cases with higher values for urinary estrogens and androgens respond better to adrenalectomy than those with a lower excretion (Huggins & Dao, 1954, Dao & Huggins, 1955, Birke et al., 1954, 1955). The clinical and metabolic responses of the cancer patients to administration of steroid hormones are also being studied from this point of view. Pearson et al. (1953, 1954) have demonstrated an increase in urinary calcium after estrogen administration to women with estrogen-dependent breast cancer. Huggins (Huggins & Dao, 1953) believes that the hormone-dependent breast cancers usually have special histological characteristics, i.e. that they are of a more differentiated type. However, this view is not in agreement with the findings of Pearson (1956a) in adrenalectomized and of ourselves in hypophysectomized breast cancers (Luft & Olivecrona, 1955).

At present, no definite criteria for the selection of cases are available. It seems, however, that a previous response to other forms of endocrine treatment, and especially castration, increases the chances for new remissions after adrenalectomy and hypophysectomy (Pearson, 1956a).

Much more work is needed before we can arrive at any prediction as to the response of cancer patients to endocrine treatment. This applies especially to cancer of the female breast. The high percentage of response of male patients
with breast and prostatic cancer to hormonal measures (estrogens and/or castration) makes a method of selection less important in this sex.

As to the second question, i.e. the choice of method of treatment, it seems that in women with metastatic breast cancer, oophorectomy in the premenopausal administration of estrogens in the postmenopausal cases would be the appropriate methods to start with. When these measures are ineffective, other methods of endocrine treatment, such as administration of androgens or ablation of the adrenals or hypophysis, should be considered. Some authors have used hypophysectomy or combined oophorectomy and adrenalectomy as a primary therapeutic procedure in metastatic cancer in women. It remains to be investigated, whether the total duration of the remission is longer when these measures are used after previous castration or estrogen treatment than when used primarily. This point is of great practical importance.

When cancer growth continues or is reassumed after adrenalectomy or hypophysectomy hormone administration seems to be of no value. Such treatment has been tried after hypophysectomy (Luft et al., 1956) and after adrenalectomy (Dao & Huggins, 1955), being in all instances without effect.

As a tentative schedule for the endocrine treatment of metastatic breast cancer the following is suggested:

<table>
<thead>
<tr>
<th>premenopausal</th>
<th>postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. oophorectomy</td>
<td>1. estrogens</td>
</tr>
<tr>
<td>(2. androgens)</td>
<td>(2. androgens)</td>
</tr>
<tr>
<td>3. adrenalectomy or hypophysectomy</td>
<td>3. adrenalectomy + oophorectomy</td>
</tr>
<tr>
<td></td>
<td>or hypophysectomy</td>
</tr>
<tr>
<td></td>
<td>4. hypophysectomy</td>
</tr>
</tbody>
</table>

For metastatic cancer of the prostate the tentative schedule would be as follows:

| 1. estrogens and/or castration    |
|                                   |
| (adrenalectomy)                   |
| 2. hypophysectomy                 |

From this review it is obvious that, despite numerous reports, many important questions have to be answered before we get an accurate knowledge of the relation between hormones and cancer. There are very few studies in
which the same observer has compared the effects of different methods of endocrine treatment.\(^{a}\) We are still lacking studies on the complete endocrine status of cancer patients before, during and after different kinds of endocrine treatment. Such clinical studies are the more important since extrapolation of results from experimental work in animals to man might be misleading. Measurement of hypophyseal hormones would help to elucidate the role played by the hypophysis on cancer in man.

**SUMMARY**

The usual methods for endocrine treatment of metastatic cancer of the breast and prostate are reviewed. The results obtained with the different procedures, when the percentage and duration of objective remissions were used as a criteria, are presented. The role of hormones other than estrogens and androgens in the growth of cancerous tissue of breast and prostate is discussed.

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