THE SURGERY OF THE ENDOCRINE SYSTEM IN CARCINOMA OF THE BREAST

By JOHN HADFIELD, M.S., F.R.C.S.

Senior Lecturer, Surgical Professorial Unit, St. Bartholomew's Hospital

In this article an attempt will be made to summarize our views on the value of excision of endocrine glands in the control of metastatic breast cancer.

Metastatic cancer may be treated either by excision of endocrine glands (surgical deprivation) or administration of hormones (addition therapy). This article deals only with deprivation. Addition will only be considered as it directly affects deprivation and not as a method of therapy in its own right.

The purpose of surgical deprivation is to terminate the production of the specific hormones essential for the proliferation by mitosis of normal mammary epithelium and presumably of the malignant growths arising in this epithelium. The pituitary hormones concerned are probably prolactin and somatotrophin. This combination may be non-committally labelled as the 'mammothrophic principle.' Pituitary ablation apart from removing this will remove the trophic control exercised by the pituitary over the ovaries and adrenals and in that way cause a depression of their function and a lowering of oestrogen production (see Figs. 1 and 2).

The purpose of bilateral oophorectomy and adrenalectomy is to abolish the production of the steroid hormones oestrogen and progesterone. As it is thought that a third hormone, progestational in nature, forms the third partner controlling normal and cancerous mammary growths. Progestational hormone production is abolished by adrenalectomy, or hypophysectomy which induces secondary adrenal cortical atrophy.

The concept of control of breast growth by a triad of hormones, oestrogen, pituitary mammothrophin and progesterone is the basis of our present ideas in surgical deprivation and the existence of the hypothetical state of simple oestrogen dependence is no longer tenable for the following reasons:

First, regression induced by removal of oestrogen sources, such as the adrenals or ovaries, can be followed by exacerbation of the disease in the

absence of any significant quantity of oestrogen demonstrable in the urine or on vaginal smear. Hypophysectomy in these cases will often cause regression.⁸

Secondly, it has been shown by Pearson, New York,¹ that breast cancer in regression after hypophysectomy can be temporarily reactivated by the administration of pituitary growth hormone.

Thirdly, it has been shown by Scowen and Hadfield² that other factors present in the urine of normal pre-menopausal women and removed by hypophysectomy can stimulate breast growth. These substances are non-oestrogenic and may be either pituitary growth hormone or prolactin, or both of these hormones.³

Lastly, a study of the natural history of the disease in relation to the naturally occurring menopause gives further evidence.⁴ A comparison of the length of a remission occurring spontaneously during a naturally occurring menopause or after surgical castration is instructive: the former cases induce remissions for periods of one to four years, whereas after castration the average duration of remission is from 3 to 12 months. We consider that this difference should be attributed to the fact that during the time of the naturally occurring menopause pituitary changes and gradual subsidence of ovarian function occur together, the patient losing ovarian oestrogen and, temporarily at least, pituitary mammothrophin. Simple castration accounts for the removal of ovarian oestrogen alone, without a simultaneous effect on the pituitary.

Oophorectomy

This has its greatest value in the pre-menopausal patient. It should, at the same time, be combined with a careful search for metastases in the abdominal cavity, including the liver. Opinion varies as to what age oophorectomy should be done. We consider that it should be limited to a single procedure in patients before the menopause while the patient is still menstruating. Our reasons for this are as follows: First, in published series of patients

Diagrams to show the control of normal breast growth and development by the mammogenic triad—oestrogen, progesterone and growth hormone

FIG. 1.—Pre-menopausal woman.

FIG. 2.—Post-menopausal woman (Adrenal 'Take-over').

castrated while they are still menstruating the regression rate is very much higher than it is after menstruation has ceased. In other series where it is possible to divide the pre- and post-menopausal cases and then re-evaluate the results, it will be seen that the discrepancy in the figures disappears when the post-menopausal cases are eliminated. Studies of the effects of oophorectomy in post-menopausal patients show such a poor rate of relief that the single procedure must be regarded as of questionable value in these circumstances.

The rationale of oophorectomy is that a major source of oestrogen production is removed. In a pre-menopausal woman where the pre-operative oestrogen level is high, oophorectomy will cause a very marked fall in the oestrogen level, but will not eliminate oestrogen production completely. This fall in oestrogen may be accompanied by regression of the disease and this will persist until the oestrogen level becomes again raised when the adrenal takes over oestrogen production. There are, however, examples where the disease is unchecked by oophorectomy in spite of an oestrogen fall.⁵

In studies of oestrogen levels in post-menopausal women before and after oophorectomy we have consistently failed to show any significant change in oestrogen level after operation. For this reason we do not advise oophorectomy as a single procedure in the post-menopausal woman.

Adrenalectomy

The rationale for adrenalectomy, like oophorectomy, is to lower or abolish oestrogen production. For this reason it can be of no use when there is little or no oestrogen present. Of all the methods for measuring oestrogen production the cytology of the vaginal smear provides reasonably accurate information and can easily be carried out in the average hospital laboratory.⁶ It would seem advisable to gain some impression of oestrogen production before proceeding to adrenalectomy. By this means we consider that a number of cases obviously doomed to failure will be eliminated. Although a very much longer success rate will be obtained if only cases where there is a high or moderate oestrogen level present are selected for adrenalectomy, some patients in this group will fail to respond in spite of a considerable fall in oestrogen level post-operatively.⁷

We advise adrenalectomy in the following circumstances:

1. When progression of disease follows a growth regression induced by previous oophorectomy in the pre-menopausal period.
2. If, before the menopause, oophorectomy or addition therapy have failed to induce regression

of disease and if oestrogen is demonstrable on vaginal smear.

3. When a woman continues to produce oestrogen after the menopause. Many people combine this operation with removal of the ovaries on the assumption that the post-menopausal ovary produces oestrogen. Although we would doubt the utility of removing the ovaries in such patients, this is the practice of many surgeons, and at least has the value of giving the operator a chance to search the abdomen, and especially the liver, for demonstrable metastases, for this may be a useful guide in the choice of subsequent therapy.

We consider that hepatic or intraperitoneal metastases respond poorly on the whole to surgical deprivation. In a pre-menopausal patient whose ovaries have been removed or in the post-menopausal woman when adrenalectomy is under consideration, we would consider performing a peritoneoscopy in doubtful cases so that the liver and peritoneal cavity may be examined.

Hypophysectomy

The aim of this operation is to abolish the production of those hormones concerned with normal mammogenesis, together with the trophic hormones ACTH and gonadotrophin, which control the production of oestrogen by the adrenal and ovary. For surgical hypophysectomy the services of an experienced neuro-surgeon are required. Attempts have been made by some general and E.N.T. surgeons to either remove the pituitary by the trans-sphenoidal route or to destroy it by the implantation of radon or yttrium seeds. These methods seldom produce complete hypophysectomy. This can be effected, we believe, by a competent neuro-surgeon who has studied the technique.

The patients suitable for hypophysectomy may be grouped as follows:⁸

1. Patients with progressive disease in whom oestrogen production is low or has ceased as judged by vaginal smear and who may or may not have had previous hormone deprivation. A low level of oestrogen production may follow the previous removal of ovaries and/or adrenals and there may have been a temporary regression of tumour growth, followed later by progressive disease in spite of a low oestrogen value.
2. Patients having progressive disease following oophorectomy and adrenalectomy. These measures may or may not have induced regression, but at the time of evaluation the oestrogen level is moderate or high.

The problem is not so clearly defined as this simplified description would indicate and each case must be judged on its merits. The indications for oophorectomy in metastatic breast cancer seem

clear. The choice between adrenalectomy or hypophysectomy in the presence or absence of oestrogen is also a relatively simple issue. In some centres, partly for the purpose of evaluation of the method and also in the hope of obtaining longer relief by abolishing the production of pituitary protein hormones as well as steroids, hypophysectomy has been used in place of adrenalectomy even in the presence of considerable quantities of oestrogen. Results show that this operation is as effective in lowering or eliminating the oestrogen level as adrenalectomy.

There is no doubt that neither adrenalectomy nor hypophysectomy should be practised in the very old and weak or in the very ill, where even as a palliative measure they are often more lethal than the disease. In such cases addition therapy is easier and, we think, has as much or a little more to offer.

It is true that regressing metastases follow Cade's all-or-none law, in which he states that if regression is obtained by excision of endocrine sources in a case of breast cancer, this will occur at all sites of metastases. From our personal observations, however, we feel that either hypophysectomy or adrenalectomy is contraindicated in patients with gross peri-bronchial pulmonary spread, brain metastases, gross liver involvement or submucous oesophageal spread causing dysphagia.

Published results suggest that the length of average remission after hypophysectomy may be longer than after adrenalectomy. The results, in general, in selected cases are comparable and as

adrenalectomy can be practised by a general surgeon it would seem right at present to advise it when oestrogen is present in fair quantity.

Prophylactic Operations

For a long time surgeons have been disappointed by the large number of breast cancers recurring after adequate local therapy by radical mastectomy, irradiation or a combination of the two. For this reason prophylactic castration at the time of local treatment has been tried in several centres. Full data and an adequate length of time for follow-up has not yet elapsed, so that selection remains at present a matter for careful clinical judgment.

Many surgeons still prefer to limit surgical deprivation to the patients with developed metastases, for whom temporary palliation can be effected by endocrine ablation. This would certainly seem desirable with hypophysectomy and adrenalectomy in our present state of knowledge.

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