ADRENALECTOMY IN BREAST CANCER AN ATTEMPT TO CORRELATE CLINICAL RESULTS WITH OESTROGEN PRODUCTION

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Continued excretion of oestrogen produced by the adrenal cortex occurs after oophorectomy in the majority of women with breast cancer. In 1945 Huggins and Scott performed bilateral adrenalectomy in four cases of advanced breast and prostatic cancer in an attempt to remove the second source of oestrogen production from the body. One patient survived for 116 days in a hypo-adrenal state, with some objective improvement in skeletal metastases. When cortisone became available the operation was carried out in 18 cases (Huggins and Bergenstal, 1952). Seven were women suffering from cancer of the breast, and clinical improvement was induced in all of them. The results stimulated great interest in the subject, and since 1952 many series of cases have been reported. It seems that bilateral adrenalectomy can play a definite and sometimes valuable part in the palliative treatment of breast cancer.

When adrenalectomy fails to induce a growth regression in breast cancer, oestrogen independence is generally assumed to be the cause. A second possible explanation was suggested by the reports of Scowen (1955) and of Struthers (1956), who found that oestrogen secretion could continue after bilateral adrenalectomy, as judged by the appearance of the vaginal smear. This was an unexpected result at that time, but these findings have since been confirmed by urinary oestrogen estimations, using Brown's (1955) chemical method (Greenwood and Bulbrook, 1956; Bulbrook and Greenwood, 1957), and also by biological assay (Dao, 1957; Bulbrook *et al.*, 1958c).

We have been unable to find any published reports in which an attempt has been made to correlate oestrogen excretion with the patient's clinical state after adrenalectomy. This paper reports such a survey of 13 cases of metastatic breast cancer in women treated by bilateral adrenalectomy.

Methods

Chemical.—The chemical method of Brown (1955) for the determination of urinary oestrone, oestradiol-17 β , and oestriol was used initially. This technique gives an underestimate of the amount of oestradiol-17 β and oestriol when cortisone is administered to the patient. A minor modification removes this source of interference, but a variety of drugs and aperients can lead to an overestimate of the amount of oestrogen in the urine (Brown *et al.*, 1957). Oestrogen excretion is recorded as zero when the amounts detected are below the limit of sensitivity of the chemical

method. This is an arbitrary limit which can be lowered by the more sensitive biological assay (Bulbrook *et al.*, 1958c).

Clinical.—In this series regression is defined as objective improvement in either surface lesions or in deep metastatic lesions visualized by radiography. Clinical assessments were carried out without prior knowledge of the biochemical results. The patient's age quoted is that at the time of adrenalectomy. Thirteen patients with metastatic breast cancer were studied; in seven cases urinary oestrogen estimations were carried out before and after adrenalectomy and at intervals after operation; in the remaining six, only post-operative estimations were carried out.

The cases are divisible into two groups: those in objective remission, and those in relapse.

Oestrogen Excretion in Patients During Objective Remission

Of the 13 patients studied, only three were in remission at the time the oestrogen estimations were carried out. The detailed results are described below.

Case 1 (Fig. 1).—The patient, aged 48, was married. Ten years after left radical mastectomy the wound ulcerated. Seven years later, when she was 46 years old, she was treated by oophorectomy, with some benefit for six months, although the wound did not completely heal. Two years later there was gross ulceration of the chest wall spreading into the axilla; there was no evidence of distant metastases. Bilateral adrenalectomy was performed and induced

FIG. 1.—Case 1.—Excretion of oestrogen before and after bilateral adrenalectomy. In Figs. 1, 2, and 4 the day of operation is marked with a vertical arrow. In all Figs. the oestrogen excretion is shown as total oestrogen—the sum of the oestrone, oestradiol-17 β , and oestriol values. Each vertical column gives the mean of a duplicate determination on a 24-hour specimen of urine. Open circles on the abscissa indicate no detectable oestrogen.

regression of the growth, which has been maintained for eight months. Before adrenalectomy the mean total oestrogen level was 3.7 μ g./24 hours; after operation zero levels were frequent, with occasional small amounts of oestrogen found in some specimens of urine. At subsequent follow-up at intervals after operation, oestrogen was occasionally detected in the urine. Thus in this case regression of the tumour was associated with the virtual disappearance of oestrogen from the urine.

Case 2 (Fig. 2).—This patient, aged 42, married, underwent oophorectomy three and a half years after radical mastectomy because of the appearance of metastases in the left axilla and supraclavicular glands. There were no pulmonary or skeletal secondaries. The operation led to a short symptomatic regression, but skeletal secondaries ultimately developed. Two years and nine months after oophorectomy, bilateral adrenalectomy was carried out. An objective remission was induced. This lasted for four months, during which time a pathological fracture of the ulna healed and secondary deposits in the skull became smaller and calcified. During this period oestrogen excretion was reduced but not entirely abolished. Zero values were uncommon, and the mean total level of oestrogen over the first post-operative month was 1.9 μ g./24 hours.

At a subsequent examination, eight months later, the disease was progressive, metastases being present in the clavicles, spine, lung, and brain. At this time oestrogen excretion had risen to a relatively high level and was persistent (mean total = 8.5 $\mu\text{g.}/24$ hours). Two months before death—which occurred 11 months after adrenalectomy—only one

FIG. 2.—Case 2. Excretion of oestrogen before and after bilateral adrenalectomy.

of three urine specimens contained detectable amounts of oestrogen. This case illustrates the transition from regression to relapse. During the short remission oestrogen excretion was persistent and rose considerably in relapse until just before death.

Case 3.—From this patient, a married woman aged 46, no pre-operative specimens were obtained. A radical mastectomy was performed at the age of 45. Ten months later skeletal metastases developed, and at oophorectomy, which had no effect, liver secondaries were found. Adrenalectomy was carried out three months later and led to an objective regression of both skeletal and hepatic metastases. During the period of regression oestrogen estimations were carried out 15 and 40 months after operation. No oestrogen was detected in any of the 11 specimens analysed. Four years after adrenalectomy there was evidence of progressive disease. Seven analyses were carried out, and in only one was there detectable oestrogen (approximately 1.5 $\mu\text{g.}$ of oestriol). Unlike Case 2, the transition from remission to relapse was not accompanied by a rise in oestrogen excretion.

In these three cases the period of remission was associated with either no detectable oestrogen (Case 3) or with a negligible and spasmodic excretion (Case 1). Case 2 shows that the continued excretion of oestrogen, admittedly small, is not incompatible with objective remission. Progression in this case was accompanied by a rise in oestrogen excretion but in Case 3 this did not occur.

Oestrogen Excretion in Patients During Relapse

This group includes patients whose oestrogen excretion was studied before and after adrenalectomy but who had no benefit from the operation, and those who were only studied when in relapse. Two examples are described in detail.

Case 4.—This patient, aged 51, married, was treated by radical mastectomy at the age of 51, when she was one year post-menopausal. Nine months later oophorectomy and adrenalectomy were carried out because of recurrence of the local growth. The operation led to the cessation of oestrogen excretion, but the patient died of progressive disease four months after operation. The oestrogen results are shown in Fig. 3.

FIG. 3.—Case 4. Excretion of oestrogen before and after bilateral oophorectomy and adrenalectomy. The first vertical arrow indicates the time at which bilateral oophorectomy and single adrenalectomy was carried out; the second arrow indicates the time of removal of the second adrenal gland.

In a similar case (No. 6, see Table) with a very high post-oophorectomy oestrogen level (13.8 $\mu\text{g.}/24$ hours), oestrogen excretion was abolished by operation, but no clinical effect was noted.

Case 5 (Fig. 4).—This patient, aged 38, married, was treated by oophorectomy at the age of 37, 20 months after mastectomy, because of multiple skeletal deposits. Four

FIG. 4.—Case 5. Excretion of oestrogen before and after bilateral adrenalectomy.

Oestrogen Excretion Before and After Bilateral Adrenalectomy*

Group	Case No. and Age	Pre-Adrenalectomy				Post-Adrenalectomy							
		O	D	T	Total	In Remission				In Relapse			
						O	D	T	Total	O	D	T	Total
1	1 (48)	1.5	0.0	2.2	3.7 (9)	0.5	0.0	0.0	0.5 (7)	0.9	0.7	3.0	4.6 (12)
	2 (42)	4.5	1.4	2.8	8.7 (2)	1.3	0.6	0.0	1.9 (8)	0.0	0.0	0.0	0.0 (7)
	3 (46)					0.0	0.0	0.0	0.0 (11)	0.0	0.0	0.0	0.0 (7)
2	4 (51)	2.8	0.3	0.0	3.1 (5)					0.9	0.9	3.6	5.4 (10)
	5 (38)	1.8	1.4	0.0	3.2 (2)					0.0	0.0	0.0	0.0 (2)
	6 (43)	4.9	4.3	4.6	13.8 (4)					0.5	0.0	1.3	1.8 (7)
	7 (66)	1.0	0.0	2.2	3.2 (5)					1.3	0.8	7.3	9.4 (24)
	8 (44)									0.9	1.0	0.4	2.3 (7)
	9 (47)									0.0	0.0	1.1	1.1 (4)
	10 (37)									0.0	0.0	0.0	0.0 (7)
	11 (46)									0.0	0.0	0.0	0.0 (5)
	12 (52)									0.0	0.0	0.0	0.0 (5)
	13 (46)									0.0	0.0	0.0	0.0 (5)

*The case numbers are those referred to in the text; the age of the patient at adrenalectomy is given in parentheses in the first column. O, D, and T refer to oestrone, oestradiol-17 β , and oestriol respectively, and the figures given are arithmetical means. Figures in parentheses in the columns headed "Total" refer to the number of estimations carried out. All results are expressed in $\mu\text{g.}/24$ hours.

All patients had been previously oophorectomized, with the exception of Cases 4, 11, and 13, who were subjected to bilateral oophorectomy and adrenalectomy at the same time.

months of objective remission followed and a pathological fracture of the humerus consolidated. Thereafter the disease progressed and adrenalectomy was carried out. No benefit was obtained, and the patient died of progressive disease 22 months after operation. It can be seen from Fig. 4 that bilateral adrenalectomy had virtually no effect on oestrogen excretion.

A further seven patients were studied in relapse. In four oestrogen was found in the urine, in one case in remarkably high amounts—up to 50 $\mu\text{g.}/24$ hours. This abnormal level of excretion was followed by a period when the patient excreted over 9 $\mu\text{g.}/24$ hours. This level, subsequently confirmed by quantitative biological assay, is greater than the mean amount of oestrogen produced by the adrenal glands and excreted in the urine of post-menopausal women.

In the 10 cases described in this section, five either derived no benefit from adrenalectomy or, when the oestrogen estimations were carried out, were in relapse and not excreting detectable amounts of oestrogen. The remaining five were excreting oestrogen whilst the disease was progressing. A summary of the findings for the 13 patients is presented in the Table, in which the mean total pre-operative oestrogen values are given and the mean levels found in relapse or in remission are also shown. It must be pointed out that the mean figures should be accepted with some reserve. Reference to Figs. 1 and 2 shows the intermittent nature of oestrogen excretion after adrenalectomy, and from this it can be concluded that the estimation of the oestrogen content of single 24-hour specimens of urine may be misleading. Short periods, during which oestrogen excretion is relatively high, may be followed by periods during which little oestrogen can be detected. This phenomenon therefore reduces the value of a mean figure. Nevertheless, the table illustrates the mean excretion before operation and the extent to which adrenalectomy causes a diminution in excretion. The mean pre-operative figure is within the range given for post-menopausal women or oophorectomized women with cancer of the breast given in a previous paper (Bulbrook *et al.*, 1958a). Average oestrogen levels in remission are less than 1 $\mu\text{g.}/24$ hours (total), with a considerable increase when the levels in relapse are considered.

Discussion

It must be emphasized that the series of patients described is small and that of a total of 13 cases six were studied only during relapse. Any conclusions based on the results must therefore be tentative.

It is clear that adrenalectomy reduces, even if it does not always abolish, oestrogen excretion. There is a significant difference between the mean pre-operative level and the mean post-operative level for the patients shown in the Table. This affords clear evidence that the post-oophorectomy or post-menopausal excretion of oestrogen described in a previous paper (Bulbrook *et al.*, 1958a) is of adrenal origin in the human (see Brown, 1958). Remission of the disease, however, does not always follow the reduction or abolition of oestrogen excretion.

It seems that continued oestrogen excretion is not necessarily exclusive of objective regression of the disease. The amounts excreted by Case 1 after operation were negligible and inconstant, but Case 2 showed a definite and persistent excretion. If this result can be confirmed by a wider study on more cases, the implication is that the cessation of secretion of hormones other than the oestrogenic steroids produced by the ovaries and adrenals may be decisive in causing the regression of human breast cancer. The complex nature of the dependence of normal breast growth on a group of hormones acting together is well established in experimental animals (see, for example, Lyons *et al.*, 1955; Hadfield, 1957), but such data are almost entirely lacking for the human. The participation of a pituitary factor is suggested by the finding that two patients (Cases 11 and 13) in relapse after adrenalectomy were without detectable oestrogen but obtained remission after subsequent hypophysectomy (Bulbrook *et al.*, 1958b).

Half the patients in relapse in this series showed continued excretion of oestrogen after adrenalectomy, compared with roughly one-third in a larger series studied without consideration of clinical state (Bulbrook and Greenwood, 1958). It seems unnecessary to postulate oestrogen independence of the tumour as the cause of the failure of treatment in these cases. In considering the six patients in relapse in whose urine no oestrogen could be detected, some caution must be used before continued tumour growth is ascribed to oestrogen independence or to dependence upon pituitary factors. With the use of the more sensitive biological assay (Bulbrook *et al.*, 1958c) it has been shown that oestrogen excretion may continue in some oophorectomized adrenalectomized patients, although in amounts not detectable by the chemical method.

The source of the continued oestrogen remains obscure. The literature describes the occurrence of microscopical ectopic adrenal tissue, but no macroscopic rests have been found after death in four of the patients in this series. One (Case 8) was excreting considerable amounts of oestrogen. Furthermore, Strong *et al.* (1956) could not elicit an increased oestrogen excretion by the administration of adrenocorticotrophin in adrenalectomized patients. On the other hand, Bulbrook and Greenwood (1958) have found that continued oestrogen excretion after adrenalectomy tends to be present with the continued excretion of androsterone and aetiocholanolone, compounds which are not considered to be derived from administered cortisone. This result therefore indicates that the probable source of the steroid hormone production is likely to be adrenal tissue; otherwise it is necessary to postulate an alternative source with adrenal-like properties.

It has also been suggested that the tumour itself may be responsible for the production of oestrogens. Chemically and biologically detectable amounts of oestrogens have been found in all cases in a series of adrenalectomized patients with diffuse carcinomatosis (Daniel and Mitchell, personal communication). This theory is supported to a certain extent by the results in this paper, which show that oestrogen excretion may be associated with progression of the disease. In a previous paper (Bulbrook *et al.*, 1958a) oestrogen excretion rose as the disease progressed in a patient following oophorectomy until, just before death, relatively enormous amounts of oestrogen were recorded (four times the mean post-oophorectomy level). These results could be interpreted as indicating tumour production of oestrogen. Similarly, in Case 8 (see Table) the mean oestrogen level after oophorectomy and adrenalectomy was almost twice that found for patients after oophorectomy alone. In this patient a careful search at post-mortem examination failed to reveal macroscopic adrenal rests. If the tumour itself produces oestrogen, this does not occur in all cases of progressive disease (see Cases 3, 4, 6, 11, 12, and 13 in the Table), where no oestrogens were detected by the chemical method.

Finally, oestrogen analyses of urine obtained from patients after adrenalectomy afford no reliable guide to the clinical state of individual patients. Every permutation may occur, remission or relapse being accompanied in some cases by oestrogen excretion, while in others no oestrogens were detectable. Only when the patients in this small series are considered as a group does it appear that there is a tendency for remission to be accompanied by low or zero excretion and for relapse to be associated with higher levels of excretion.

Summary

The effect of adrenalectomy on both the clinical state and oestrogen excretion has been studied in 13 women with metastatic breast cancer.

Bilateral adrenalectomy caused a marked reduction in the amount of oestrogen excreted, but complete abolition of excretion was not always achieved. However, continued oestrogen excretion did not exclude objective regression.

Conversely, progression of the disease might take place in spite of the fact that no oestrogen could be detected in the urine. In general, continued oestrogen excretion was found more often in cases in relapse than in remission.

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In 1953 Luft and Olivecrona reported that hypophysectomy was an effective means of palliation in a significant proportion of cases of metastatic breast cancer. Subsequent work has confirmed these results (Luft and Olivecrona, 1955; Pearson *et al.*, 1955). The beneficial effects of the operation were ascribed to the inhibition of ovarian and adrenal function due to the removal of the relevant pituitary trophic hormones, and to the removal of those pituitary hormones which might have a direct influence on human breast cancer.

The technical difficulties in totally removing the pituitary gland are formidable, and reports on post-mortem findings suggest that complete removal is infrequently achieved (Hortling *et al.*, 1957; Luft *et al.*, 1958). Post-operative investigations of the living patients are therefore of value in deciding if removal has been complete; and, whilst methods are available for the bio-assay of pituitary gonadotrophin and for measuring the functional capacity of the thyroid, adrenals, and ovaries, it is possible that repeated oestrogen measurements provide reliable information on pituitary function following attempted ablation

(Dodds *et al.*, 1956). It has been shown (Greenwood and Bulbrook, 1956, 1957) that many patients still excrete appreciable quantities of oestrogen in the urine after hypophysectomy, but no correlation of these or subsequent results with the clinical state and/or the post-mortem findings has been attempted.

The present paper reports an effort to correlate oestrogen excretion with the clinical state of 16 breast-cancer patients on whom hypophysectomy was performed.

Methods.—The clinical and chemical methods were exactly as described in previous papers (Bulbrook *et al.*, 1958a, 1958b).

In the 16 patients studied, oestrogen estimations were carried out before and after operation. The results have been divided into groups: the first showing oestrogen levels found in 11 patients who obtained regression at hypophysectomy, the second showing the oestrogen levels in the five patients who derived no benefit from surgical hypophysectomy. One in the latter group was a male. The ages given refer to age at hypophysectomy.

Oestrogen Excretion in Patients in Whom Objective Remission of Growth was Induced by Hypophysectomy

Of the 11 patients included in this group, five were post-menopausal, four had previously been treated by oophorectomy, and two by oophorectomy and adrenalectomy. All but two (Cases 1 and 11) had undergone radical mastectomy. Remission of the disease varied from 2 to 16 months after hypophysectomy, and in five patients remission has continued to the time of writing. Oestrogen studies were carried out before operation and at least one month after operation—with one exception, Case 4. The mean oestrogen levels were calculated from serial analyses of 24-hour specimens of urine. Table I summarizes the clinical and biochemical findings of the 11 patients studied in this section, and the salient features of the cases are considered in detail below.

Case 2 (Fig. 1).—This patient, aged 55, had a ten-years history of breast cancer treated in turn by mastectomy, deep x-ray therapy, and cortisone. At hypophysectomy, when

FIG. 1.—Case 2. Excretion of oestrogen before and after hypophysectomy. In Figs. 1–4 the day of operation is marked with a vertical arrow; oestrogen excretion is shown as total oestrogen—the sum of the oestrone, oestradiol-17 β , and oestrial values. Each vertical column gives the mean of a duplicate determination on a 24-hour specimen of urine. Open circles on the abscissa indicate no detectable oestrogen.

aged 55, she was three years post-menopausal. She had metastases in the lumbar spine, an ulcerated chest wall, and skin nodules in the neck. Oestrogen excretion was low compared with the mean level for post-menopausal women with breast cancer and was reduced in the first post-operative month to levels indistinguishable from zero. Growth regression followed hypophysectomy, and this has continued up to the time of writing, 15 months after operation. Follow-up specimens obtained 13 months after operation showed the continued absence of oestrogen in the urine. The