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.

We are grateful to the surgical staff and the staff of the radiotherapy department of St. Bartholomew's Hospital for allowing us to investigate patients under their care, and particularly to Professor Sir James Paterson Ross, who has also been most helpful with his advice and criticism.

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HYPOPHYSECTOMY IN BREAST CANCER

AN ATTEMPT TO CORRELATE CLINICAL RESULTS WITH OESTROGEN PRODUCTION

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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

oestrogen excretion in this patient (Fig. 1) illustrates the expected effect of hypophysectomy in abolishing oestrogen excretion.

In five further cases (Nos. 1, 3, 4, 6, and 8) a similar unequivocal fall to zero in oestrogen excretion was found after the first post-operative month, accompanied by regression of the disease.

Case 4 (Fig. 2).—This patient, aged 65, was studied within two weeks of operation, and oestrogen was detectable in the urine in amounts greater than those found before

FIG. 2.—Case 4. Excretion of oestrogen before and after hypophysectomy.

FIG. 3.—Case 5. Excretion of oestrogen before and after hypophysectomy.

operation. This increase in oestrogen was confirmed by biological assay. No oestrogen was detected three weeks after operation, and follow-up specimens at nine weeks and 14 months suggest that the fall to zero continued. Skin and glandular metastases decreased after operation, and remission has been maintained up to the time of writing, 16 months after operation.

Case 5 (Fig. 3).—In this patient, aged 42, an initial fall of oestrogen excretion to zero was associated with regression of cutaneous and skeletal lesions. Although this marked regression continued, oestrogen was detected in the urine for a short period some three months after operation. Biochemical estimations of urinary oestrogens, confirmed by biological assay, showed that the predominant urinary steroid was oestriol with trace amounts of oestrone. The total amount of oestrogen was equivalent to that found in normal menstruating women, and eight times the mean pre-operative level. In this case it would seem that regression of the disease following hypophysectomy is not invariably accompanied by a persistent fall in oestrogen excretion to zero.

Case 7.—This patient, aged 44, showed little fall in total oestrogen after hypophysectomy with remission of the disease: oestrogen was detectable in three of six specimens collected after operation.

Case 9.—In this patient, aged 40, hypophysectomy was accompanied by a remission of skeletal metastases, and this has continued to the time of writing, 15 months after operation, in the absence of detectable oestrogen. Hypophysectomy in this patient reduced oestrogen excretion to levels indistinguishable from zero by the chemical method used, but oestrogen was detectable on one occasion, one month after operation, by the more sensitive biological assay.

Two patients were studied with progressive disease after a previous oophorectomy and adrenalectomy. Case 10 had not benefited from this treatment, while Case 11 had been in regression for two years before exacerbation of breast and skin symptoms occurred. Oestrogen was not detectable either before or after operation, which was followed by remission of symptoms for three months in both cases. The disease thereafter progressed in Case 10, death taking place four months after operation. In Case 11, however, mastectomy had not been performed and the patient was still in regression up to the time of death from an acute bacterial infection following post-operative necrosis in both the involved breasts.

Mastectomy had not been performed in Case 1 and a marked regression of growth of the breast tumour accompanied a fall in oestrogen excretion at hypophysectomy. This

TABLE I.—Oestrogen Excretion by Patients in Objective Remission after Hypophysectomy*

Case No.	Age	Pre-Hypophysectomy					No. of Analyses	Post-Hypophysectomy							
		Mean Oestrogen, $\mu\text{g.}/24$ hrs.				Mean Oestrogen, $\mu\text{g.}/24$ hrs.				No. of Analyses	Months After Operation	Period of Regression (Months)	Survival Time in Months		
		O	D	T	Total	O		D	T					Total	
No Previous Endocrine Surgery															
1†	58	1.3	1.0	2.3	4.6	9	0.0	0.0	0.0	0.0	6	1	2	2	
2	55	0.9	0.0	1.1	2.0	4	0.0	0.0	0.0	0.0	5	1	15		
3	61	1.9	0.4	2.5	4.8	10	0.0	0.0	0.0	0.0	4	1	10	12	
4	65	0.9	0.0	0.0	0.9	7	1.3	0.7	1.5	3.5	6	1			
							0.0	0.0	0.0	0.0	16	1-14	16		
5	42	2.1	0.7	3.2	6.0	8	0.0	0.0	0.0	0.0	7	3	6		
							3.3	0.0	48.3	51.6	2				
							0.0	0.0	0.0	0.0	7				
Previous Oophorectomy															
6	50	1.6	0.6	1.0	3.2	24	0.0	0.0	0.0	0.0	1	2	5	6	
7	44	0.9	0.3	5.7	6.9	10	0.8	0.0	4.0	4.8	6	1	4	5	
8	49	1.0	0.6	3.0	4.6	2	0.0	0.0	0.0	0.0	13	1-8	11		
9	40	1.6	0.6	0.0	2.2	5	0.25	0.0	0.0	0.25	5	1			
							0.0	0.0	0.0	0.0	9	3-13	15		
Previous Oophorectomy and Adrenalectomy															
10	46	0.0	0.0	0.0	0.0	9	0.0	0.0	0.0	0.0	10	1	3	4	
11*	48	0.0	0.0	0.0	0.0	5	0.0	0.0	0.0	0.0	6	1	3	3	

*Age—That at hypophysectomy. O=Oestrone. D=Oestradiol-17β. T=Oestriol. In Cases 4, 5, and 9 post-hypophysectomy oestrogen excretion was confirmed by parallel biological assay. † Not previously mastectomized.

regression continued up to the time of death three months after operation. As in Case 11, post-mortem examination showed gross necrosis of the mass in the involved breast, and it is not improbable that death was caused by the liberation of toxins from rapid autolysis of necrotic tumour tissue.

The anticipated effect of hypophysectomy is to reduce and abolish oestrogen excretion. The overall results in this section confirm that this is generally true for women after the menopause or those who are in remission after oophorectomy. In seven of the nine patients no oestrogen could be detected after the first post-operative month, and the effect appears to be persistent. In two cases no oestrogen could be detected before operation, and oestrogen analyses, although zero after operation, provided no evidence of the completeness of the removal of the pituitary in these cases. However, in 2 of the 11 patients oestrogen was detected although remission of the disease followed operation.

If the pre-operative levels of oestrogen are considered the mean total oestrogen for the nine patients is somewhat lower than the mean level found for 39 women with metastatic breast cancer after the natural menopause or bilateral oophorectomy.

Oestrogen Excretion in Patients not Benefited by Hypophysectomy

Four women were studied in this group (Table II). All had previously been treated by mastectomy; three had undergone subsequent oophorectomy; the fourth had not menstruated for a year following a course of testosterone treatment. At the time of operation all patients showed evidence of progressive skeletal metastases, and these were unaffected by hypophysectomy. The average survival time after operation was eight months. In no case was oestrogen excretion reduced or abolished by operation. A typical example of the variation in amount and pattern of excretion is shown in Fig. 4 (Case 12). The mean level of oestrogen

FIG. 4.—Case 12. Excretion of oestrogen before and after hypophysectomy.

before operation of these four patients appears to be greater than the mean pre-operative level of the patients recorded in Table I obtaining benefit from hypophysectomy.

Of incidental interest is the fact that Case 16 was a male suffering from breast cancer with widespread metastases. Neither orchidectomy nor subsequent hypophysectomy altered the progress of the disease. The latter operation reduced but did not entirely abolish oestrogen excretion.

Discussion

The object of this study was to decide if the excretion of oestrogen was correlated with the pre- and post-operative clinical state of patients suffering from metastatic breast cancer and subjected to hypophysectomy. Although the series is small, a correlation seems clearly established, since oestrogen excretion was generally absent in urine from patients in regression after hypophysectomy and present when the operation failed to benefit the patient. In four cases in remission oestrogen was demonstrated in the urine, but this was a transitory phenomenon in three of these patients. For example, Case 4 (Table I) was excreting more oestrogen two weeks after operation than before. This patient was studied at an earlier stage after hypophysectomy than the remaining cases. The presence of oestrogen 12 to 18 days after operation, followed by a period of 14 months in which no oestrogen could be detected, suggests that it may take two weeks for the elimination of circulating pituitary and adrenal hormones.

The amounts of oestrogen detected only by biological assay in Case 9 suggest that the grouping of patients in regression showing no oestrogen excretion by the chemical method may be an arbitrary classification depending only upon the sensitivity of the chemical method. No oestrogen could be detected in the urine of Case 5 for a long period. Three months after operation relatively large amounts of oestrogens were excreted for two days; this was followed by a prolonged period when again no oestrogen could be found in the urine. In both instances the chemical results were confirmed quantitatively by biological assay. We have no satisfactory explanation for this result, but it is extremely unlikely that the oestrogen could have been derived from the diet, since a patient after adrenalectomy in the same ward and on an identical diet excreted no oestrogen during this period.

In only one patient (Case 7) did oestrogen excretion continue on the same level as before operation, and this patient had an objective regression. It may be significant that survival time and the period of regression were short. This finding is discussed later.

The first two sections in Table I show that the mean pre-operative levels for the post-menopausal and post-oophorectomy patients obtaining benefit from hypophysectomy tend to be below the mean level found for women with cancer of the breast in these categories (Bulbrook *et al.*, 1958a). The mean levels were 3.6 and 4.2 µg./24 hours (total oestrogen) respectively, compared with 5 to 6 µg./24 hours. On the other hand, the mean amount of

TABLE II.—Oestrogen Excretion by Patients Deriving no Benefit from Hypophysectomy

Case No.	Age	Pre-Hypophysectomy					Post-Hypophysectomy							
		Mean Oestrogen $\mu\text{g.}/24$ hrs.				No. of Analyses	Mean Oestrogen $\mu\text{g.}/24$ hrs.				No. of Analyses	Months After Operation	Length of Survival in Months	
		O	D	T	Total		O	D	T	Total				
Previous Testosterone Treatment														
12	41	1.9	1.6	4.9	8.4	10	1.5	1.3	3.9	6.7	19	1-2	4	
Previous Oophorectomy														
13	41	2.9	1.2	4.9	9.0	10	1.6	2.9	2.4	6.9	9	1	7	
14	49	1.9	0.4	0.0	2.3	3	0.8	2.3	7.1	10.2	13	1	9	
15	46	0.8	1.8	5.6	8.2	7	0.3	0.3	11.0	11.6	8	1	7	
Male Patient with Breast Cancer—Previous Orchidectomy														
16	59	0.4	0.3	7.7	8.4	11	1.1	0.6	0.0	1.7	4	2	8	

All patients had previously undergone mastectomy. Age—That at hypophysectomy. O=Oestrone. D=Oestradiol-17β. T=Oestriol.

oestrogen excreted by the four patients who failed to benefit from operation (Table II) was 7 μ g./24 hours—a value slightly higher than the mean level for all patients in this category, and higher than the mean pre-operative level of patients obtaining remission at hypophysectomy (Table I). There are not enough patients in the series for these findings to have any statistical significance, but there may be a tendency for patients with a low pre-operative oestrogen level to benefit from hypophysectomy while those with a high level do not. Further work is needed to check the validity of this suggestion.

In two instances patients who had been previously treated by oophorectomy and adrenalectomy were subjected to hypophysectomy. In neither case was oestrogen detected in the urine either before or after hypophysectomy, yet in both patients their objective regressions were short. Unless they were excreting amounts of oestrogen not detectable by the chemical method, these results suggest a direct participation of pituitary hormones in the maintenance of human breast cancer, as opposed to an indirect trophic effect on target organs. Similarly, in the patient already referred to (Case 7) objective regression occurred in spite of continued oestrogen excretion. Again, this result is explicable on the assumption that the levels of growth hormone, prolactin, or both had been reduced below a critical level.

In the four patients referred to in Table II the most simple explanation for the failure of hypophysectomy to influence the growth of the breast cancer is the continued excretion of oestrogens due to incomplete hypophysectomy. We have, as yet, been unable to study the transition from remission to relapse in this series. However, Hortling *et al.* (1957), using the vaginal-smear technique, found that oestrogen secretion increased simultaneously with the deterioration of the patient's clinical condition.

The explanation of failure or success following endocrine ablation for breast cancer must be largely speculative until we are able to assess directly the functional capacity of the human hypophysis with a reasonable degree of precision. The results of the investigations on the small number of patients in the present series suggest that repeated biochemical estimation of oestrogens before hypophysectomy may prove to be of some value in forecasting the clinical outcome of this operation.

Continued post-operative excretion of oestrogen, by indicating incomplete removal, suggests that no significant clinical palliation is likely to occur, while cessation of oestrogen excretion would suggest the reverse. The exceptions to these generalizations provide cogent reasons for supposing that the growth of some human breast cancers is maintained by the direct action on the tumour cells of anterior pituitary hormones.

Summary

The effect of hypophysectomy on the clinical state and on oestrogen excretion has been studied in 15 women and one man with metastatic breast cancer.

Patients obtaining regression following hypophysectomy tended to have a low pre-operative level of urinary oestrogen, and in the majority oestrogen excretion virtually ceased after operation. On the other hand, continued oestrogen excretion was not always exclusive of objective regression.

Patients deriving no benefit from operation tended to have a high pre-operative oestrogen excretion and continued to excrete oestrogen after operation.

We are grateful to the surgical staff and the staff of the radiotherapy department of St. Bartholomew's Hospital for allowing us to investigate patients under their care. We would like particularly to thank Professor Sir James Paterson Ross and Dr. A. A. G. Flemming. All the operations for hypophysectomy were performed by Mr. J. E. A. O'Connell, and we are grateful to him for allowing us to continue the observations on these patients.

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A BIOCHEMICAL CONCEPT OF TUMOUR GROWTH, INFILTRATION, AND CACHEXIA

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Among the many perplexing properties of a growing tumour is its ability to build up protein and increase in weight in a host (experimental animal or man) which is fast losing weight. This ability to obtain the precursors of its protein from the metabolic pool at the expense and to the detriment of the host has been investigated in some detail by Mider, Tesluk, and Morton (1948) (see Greenstein, 1954), and from the results they obtained with the transplantable Walker 256 tumour in growing rats they have been able to show three distinct phases in the growth history of the tumour and tumour-bearing animal. During the first stage (while the tumour is relatively small) both the tumour and the host gain weight. In the second stage the tumour alone continues to gain weight, and at an increasing rate. The host tissues in this second stage at first fail to gain weight and later may even lose weight. In the third and terminal stage (often very brief) the rate of growth of the tumour falls, and eventually the tumour itself may lose weight, although not as markedly as that of the rapidly wasting tissues of the host.

Such observations in the experimental animal, and the well-known clinical fact that tumours continue to grow even in cachectic subjects, suggest that the tumour is an autonomous entity capable of thriving irrespective of the metabolic status of the tissues of the host. It is obvious, however, that even the most autonomous neoplasm must have an adequate supply of metabolites for the purposes of growth, and if the essential metabolites are not forthcoming then the rate of growth must suffer.

The effect of dietary restriction on the incidence and rate of growth of spontaneous tumours has been the subject of much careful study. Tannenbaum and his colleagues (see review, Tannenbaum, 1947), in a series of brilliant experiments, have shown that dietetic restriction can greatly reduce the incidence of both naturally occurring and carcinogen-induced tumours in experimental animals. Indeed, some 14 different tumours have been shown to be affected in this manner, and the statistical evidence from insurance companies' records collected by L. T. Dublin in 1927 (quoted by Tannenbaum, 1947) shows that the incidence of various neo-