but no stimulation of oestrogen excretion was observed. This test may be of doubtful value as an index of the capacity of the remaining adrenal tissue to secrete oestrogens. After adrenalectomy, with relatively low doses of oral cortisone, it is possible that the secretion of endogenous corticotrophin is sufficient to cause maximal or near maximal secretion rate by any remaining adrenal tissue. Exogenous corticotrophin would thus be likely to have little or no effect.

Taylor *et al.* (1949) found elevated corticotrophin levels in the blood of untreated patients with Addison's disease, and the levels did not return to normal with maintenance doses of cortisone (Sydnor *et al.*, 1953). It is well known that the level of urinary 17-ketosteroids and ketogenic steroids found in patients with Addison's disease cannot be elevated by administration of corticotrophin. On the other hand, Sayers (1955) has reported that the high level of corticotrophin in adrenalectomized patients is reduced by treatment with cortisone.

Whatever the origin of the urinary oestrogen found in some of our patients after oophorectomy and adrenalectomy may be, its immediate source is the oestrogen of the circulating blood. The hypothesis of oestrogen independence is often invoked when a breast cancer recurs in the absence of those endocrine organs assumed to produce oestrogen. The observations recorded in this paper strongly suggest that oestrogen independence cannot be assumed until oestrogen excretion has been fully investigated.

Summary

A chemical method has been applied to a study of urinary oestrogen levels of patients undergoing bilateral oophorectomy or bilateral adrenalectomy for metastatic breast cancer. Oophorectomy reduced oestrogen excretion in premenopausal women but had no effect after the menopause. Adrenalectomy carried out after oophorectomy did not always abolish oestrogen excretion.

It is concluded that, since oestrogen excretion continues after oophorectomy and may continue after adrenalectomy, failure to respond clinically to these operations is not necessarily due to the oestrogen independence of the tumour.

We are indebted to Dr. E. F. Scowen and Dr. H. E. Archer for arranging the supply of urine specimens, and to Professor C. H. Gray for specimens from two patients. We thank Mr. D. H. Patey and Dr. J. D. N. Nabarro for permission to report on the preliminary results of joint work on the "new series" of patients.

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EFFECT OF HYPOPHYSECTOMY ON URINARY OESTROGEN IN BREAST CANCER

BY

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It has been shown that patients with breast cancer may continue to excrete oestrogen in the urine after oophorectomy, adrenalectomy, or hypophysectomy (Greenwood and Bulbrook, 1956). The detailed results of the effects of the first two operations are published at page 662 in this issue (Bulbrook and Greenwood, 1957). The present paper, based on over 200 estimations on specimens from ten women and one man, describes the effect of hypophysectomy on urinary oestrogen excretion.

Method.—The method of Brown (1955a) was used to determine the amounts of oestrone, oestradiol-17β, and oestriol in duplicate aliquots from 24-hour specimens of urine. Generally, 200-ml. aliquots were taken, but with very dilute post-hypophysectomy urine 400-ml. aliquots have occasionally been analysed. The accuracy, precision, sensitivity, and specificity of the method have been described by Brown, Bulbrook, and Greenwood (1957a). The specificity of the method has been checked in the urines obtained from one patient after hypophysectomy. There was a close agreement between chemical and biological assays of the urine in this patient (Bulbrook, Greenwood, and Williams, to be published). In some patients after hypophysectomy, maintained on cortisone, the levels of oestriol may be underestimated owing to interference in the final colour reaction. This interference is removed by an extra purification step involving saponification of the oestrogen fractions (Brown, Bulbrook, and Greenwood, 1957b).

Results

In all cases described in this paper the pituitary gland was removed surgically and the pituitary fossa was filled with Zenker's solution. The effect of hypophysectomy on the urinary oestrogen excretion of 10 patients is summarized in the Table.

Effect of Hypophysectomy on Urinary Oestrogens

Patient No.	No. of Estimations	Oestrogen Excretion Before Hypophysectomy (μg./24 Hours)				No. of Estimations	Oestrogen Excretion After Hypophysectomy (μg./24 Hours)			
		O	D	T	Total		O	D	T	Total
1	10	1·9	1·6	4·9	8·4	19	1·5	1·3	3·9	6·7
2	10	2·9	1·2	4·9	9·0	9	1·6	2·9	2·4	6·9
3	10	0·9	0·3	5·7	6·9	6	0·8	0·0	4·0	4·8
4	10	1·9	4·6	2·5	9·0	4	0·0	0·0	0·0	0·0
6	8	0·5	0·4	10·4	11·3*	4	1·0	0·6	0·0	1·6
	3	0·0	0·0	0·5	0·5					
7	22	1·9	0·2	1·7	3·8	7	0·3	0·0	0·0	0·3
						6	6·0	1·1	0·6	7·7†
8	3	1·9	0·4	0·0	2·3	13	0·8	2·3	7·1	10·2
9	7	0·8	1·8	5·6	8·2	8	0·3	0·3	11·0	11·6
10	7	0·9	0·0	0·0	0·9	5	1·3	0·6	1·5	3·4‡
						13	0·0	0·0	0·0	0·0
11	—	—	—	—	—	29	2·6	1·2	0·8	4·6

* Estimations immediately after castration.
† On testosterone.
‡ Estimations immediately after hypophysectomy.
The figures in this table refer to the mean excretion of O=oestrone, D=oestradiol-17β, T=oestriol, and their sum, the total amount of oestrogen excreted, expressed in μg. per 24 hours.

The results fall roughly into three groups. The first consists of patients in whom hypophysectomy had virtually no effect on the total amount of oestrogen excreted. Patient 1, aged 41, ceased menstruating nine months before hypophysectomy. The amount of oestrogen excreted before operation (presumably of adrenal origin) fluctuated widely from day to day (Fig. 1), but the relative amounts of

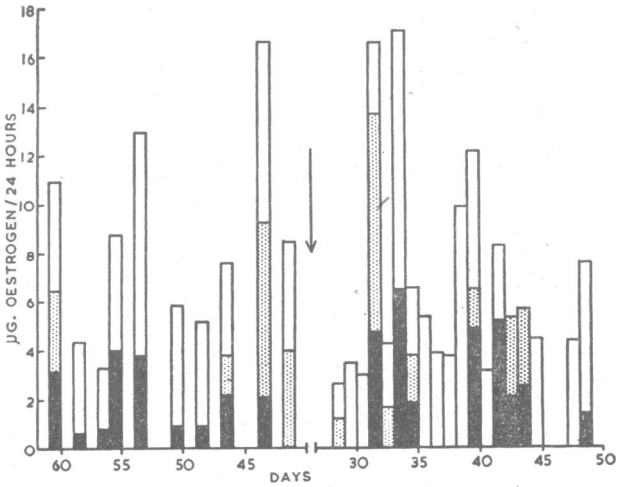

FIG. 1.—Excretion of oestrogen before and after hypophysectomy. Patient 1, aged 41; menopausal. (In all four graphs the ordinate shows the number of days or weeks before and after operation, the day of the operation being taken as day 0 and indicated by the vertical arrow. Height of vertical columns shows total amount of oestrogen excreted in 24 hours. Individual components are: black shading = oestrone, dotted area = oestradiol, white area = oestriol.)

oestrone, oestradiol, and oestriol were normal compared with the proportions found during the normal menstrual cycle (Brown, 1955b). After operation there was no change either in the pattern or in the amount of oestrogen excreted.

Patient 2, aged 39, was oophorectomized nine months before hypophysectomy. While there was little change in the total amount of oestrogen excreted after operation, a change in pattern occurred in that oestrone and oestriol were excreted in smaller amounts while the excretion of oestradiol increased. Patient 3, aged 45, was oophorectomized two years before hypophysectomy. After removal of the pituitary gland there was no significant change in either the pattern of excretion or the amount of oestrogen excreted.

The second group (Nos. 4–7) consists of patients who excreted either no oestrogen or only trace amounts after hypophysectomy. Patients 4 (Fig. 2) had not been previously oophorectomized, and the pre-operative level of excretion seemed high for a woman aged 60. Abnormal amounts of oestradiol-17β (relative to the amounts of oestrone and oestriol) were found in these specimens. After hypophysectomy no oestrogen could be found in the four specimens of urine available for analysis.

Patient 5, aged 50, had been oophorectomized three years before hypophysectomy. Twenty-four specimens of urine obtained intermittently over a period of 16 months before operation contained little oestrogen (mean = 3.2 µg. total oestrogen per 24 hours), and in the single specimen of urine available after hypophysectomy no oestrogen could be detected. Since only one analysis was possible this patient has not been included in the Table.

Patient 6, a man aged 58, had been castrated six months before hypophysectomy. Immediately after castration an average amount of 11.3 µg. total oestrogen per 24 hours was excreted over an eight-day period, but just before hypophysectomy only trace amounts of oestrogen—that is, amounts approaching the limit of sensitivity of the method—could be detected in the urine. One month after hypophysectomy trace amounts of oestrone and oestriol were found in two of four specimens of urine.

Patient 7, aged 48, was oophorectomized 11 months before hypophysectomy. After the latter operation 2 µg. of oestrone was found in one of six specimens. Later, appreciable amounts of oestrogen were found in the urine, but this oestrogen was almost certainly derived from administered testosterone (see, for example, West *et al.*, 1956).

The third group is made up of patients who showed an increased excretion of oestrogen after hypophysectomy (Nos. 8, 9, and 10).

Patient 8, aged 49, was oophorectomized three months before hypophysectomy. Only three specimens of urine were obtained before operation, and it is possible that the amount of oestrogen in these specimens may not have given a true picture of the functional activity of the adrenal glands. After removal of the pituitary gland this patient's oestrone excretion dropped to half the pre-operative level, but oestradiol excretion increased four-fold, and oestriol, absent in the pre-operative specimens of urine, was found in appreciable amounts (Fig. 3).

Patient 9, aged 46, was oophorectomized six months before hypophysectomy. Post-operatively the oestrone and oestradiol levels fell but the amount of oestriol excreted was almost doubled.

In Patient 10, a post-menopausal woman aged 64, hypophysectomy caused a temporary increase in oestrogen excretion. In four of seven specimens obtained before operation 1.5 to 2 µg.

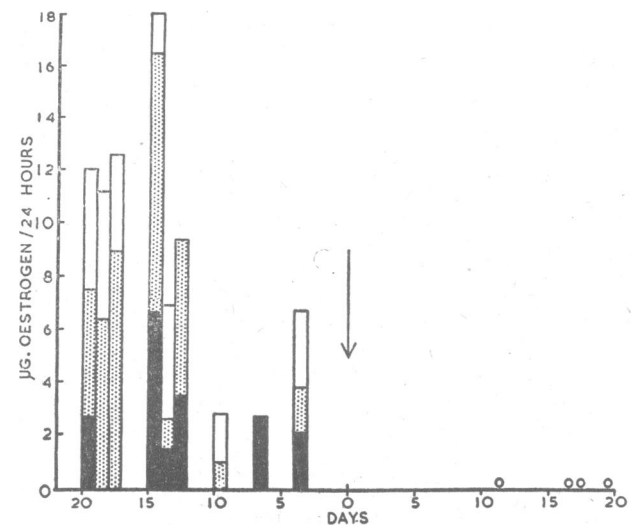

FIG. 2.—Excretion of oestrogen before and after hypophysectomy. Patient 4, aged 60; post-menopausal.

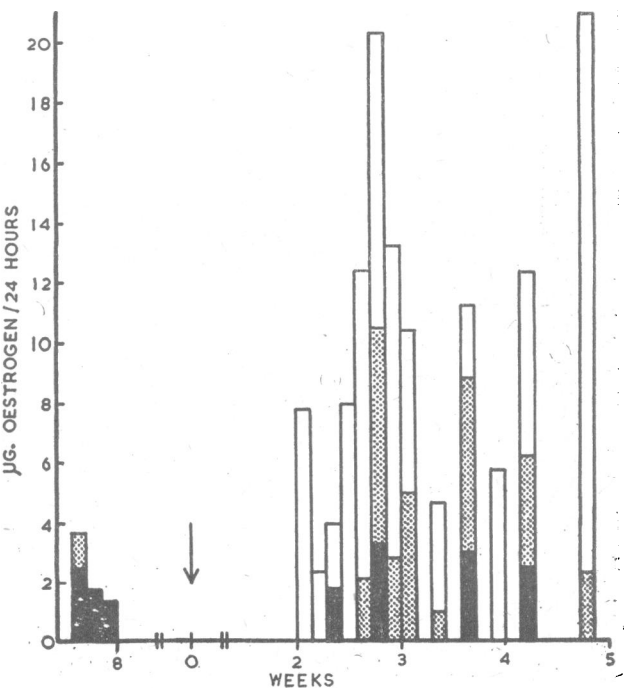

FIG. 3.—Excretion of oestrogen before and after hypophysectomy. Patient 8, aged 49; previously oophorectomized.

of oestrone per 24 hours was found. Twelve days after hypophysectomy amounts of oestrogen ranging from 2.7 to 7.4 μg. (total oestrogen per 24 hours) were found in five of six specimens. In nine subsequent assays no oestrogen could be detected in the urine.

The last patient, (No. 11, Fig. 4) cannot be grouped with the preceding ten since no pre-operative assays were carried out. However, specimens of urine were obtained intermittently between 8 and 11 months after hypophysectomy. This patient,

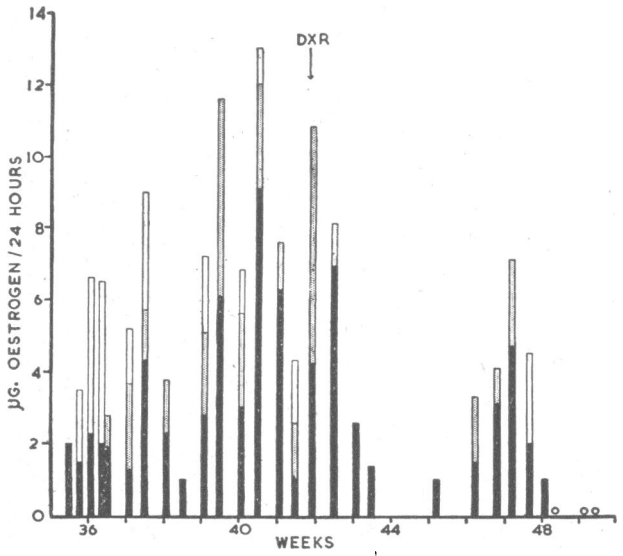

FIG. 4.—Excretion of oestrogen after hypophysectomy. Patient 11, aged 48; menopausal. DXR=deep *x*-ray treatment.

aged 48, with intact ovaries and adrenal glands, excreted between 1 and 12 μg. of total oestrogen per 24 hours over most of this period. After *x*-ray treatment there appeared to be a steady decline in the amount of oestrogen excreted, and in the last three specimens of urine available before death no oestrogen could be detected.

Discussion

The results show that oestrogen excretion continued after hypophysectomy in 7 of 11 patients in this series. If the secretion of oestrogen is controlled solely by the pituitary gland the simplest explanation of these results is that in only four cases (Nos. 4, 5, 6, and 7) was hypophysectomy effective in lowering the amount of circulating trophic hormones below that required for the continued secretion of oestrogen by the target organs. In the remaining cases enough pituitary tissue may have been left at operation to enable the target organs to function at an unchanged rate (Patients 1, 2, and 3), or rapidly regenerating tissue may have been responsible for an excessive production of trophic hormones to account for the increased excretion of oestrogen seen in Patients 8 and 9, and occurring temporarily in Patient 10.

An additional factor which may account for some part of the continued secretion of oestrogen is the presence of accessory pituitary tissue, which is often found in man (see Melchionna and Moore, 1938; Boyd, 1956). From a comparison of the histological appearance of this tissue in the presence and absence of the pituitary, Müller (1956) concluded that pharyngeal pituitary tissue in man after hypophysectomy is capable of secretory activity.

It is unlikely that the continued secretion of oestrogen was due to incomplete atrophy of the adrenal glands at the time the oestrogen estimations were carried out. Judged by 17-oxysteroid production, adrenal atrophy is complete within nine days (Luft *et al.*, 1955), but it is possible that different mechanisms for the synthesis of the various adrenal hormones may be differentially affected by removal of the pituitary gland. Most of the estimations were carried out at least three weeks after the removal of the pituitary, and Patient 11 was excreting oestrogen almost a year after operation.

Whatever the source of the oestrogen found in the urine of these patients, and whatever the factors controlling oestrogen secretion, it is clear that some caution must be exercised before the failure of a patient to respond clinically to hypophysectomy is ascribed to hormone independence of the tumour. Hormone independence cannot be assumed without appropriate measurement of hormone secretion.

Summary

In 4 of 10 patients little or no oestrogen was found in the urine after hypophysectomy. Three patients showed unchanged levels of oestrogen excretion and three showed increased levels. Yet another patient studied almost a year after operation was excreting appreciable amounts of oestrogen.

Since 7 of the 11 patients continued to excrete oestrogen after hypophysectomy, it cannot be safely assumed that a breast cancer is hormone-independent if, following operation, there is no favourable clinical response.

We are indebted to Dr. H. E. Archer and Dr. E. F. Scowen, of St. Bartholomew's Hospital, for arranging the supply of specimens of urine from nine patients, and to Mr. A. Dickson Wright, of St. Mary's Hospital, for specimens from two patients.

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ACUTE DISSEMINATED ENCEPHALOMYELITIS AND RELATED SYNDROMES

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In addition to their clinical interest the well-defined neurological syndromes which occur in the course of the acute specific fevers form a useful starting-point for a consideration of the aetiology and pathogenesis of similar syndromes encountered in other clinical contexts. There is, for example, a well-recognized resemblance between post-exanthematous encephalitis and the similar illnesses which sometimes complicate Jennerian vaccination (Miller, 1953a) and other prophylactic inoculations (Miller and Stanton, 1954a). It is tempting also to speculate on possible relationships between these syndromes and other acute demyelinating diseases in which no such clear-cut aetiological agent is evident, and to compare such naturally occurring forms with the examples of demyelinating encephalitis which have been produced in experimental animals. It is our purpose in the present paper to compare and contrast these various