tissue, the effects of the two together in "starving" the tumour may be supplementary. Equally plausible suggestions may be based on the possible katabolic effects of glucagon on the tumour itself. Both mechanisms could be involved.

The field of tumour growth is notorious for the frequency of pitfalls. We have seen no indication that the effect we are investigating is due to a contaminating infectious agent or to other artifacts. These may, of course, emerge later and necessitate a change in the interpretation of our findings. We have obtained glucagon from two sources—Indianapolis and Toronto. The various lots of insulin have been made in Toronto.

It is obvious that, if this phenomenon of the extensive inhibition of tumour growth by insulin and glucagon together is observed in a large number of other tumours in various species of animals, a clinical trial of the substances may become very tempting. Some aspects of the investigation would be easier to control in the hospital than in the experimental laboratory. Clinically the two substances *could* be given by continuous intravenous drip and the hypoglycaemia which has plagued us could be detected at an early stage. Frequent blood-sugar estimations have not been considered advisable in the small animals. A sufficient number to establish low blood sugar as the cause of death in the insulin-treated animals which succumbed have been made. A great deal more should be learned in experiments on animals before any clinical study is seriously considered. An inhibition which persists only during the administration of the substances would be of limited clinical interest. The obvious possibility of using other substances to supplement the inhibition produced by insulin and glucagon is being explored.

We are indebted to Mrs. H. Viilup, Mrs. C. Hooper, and Mr. Gunther Brunet for their efficient technical assistance. This work has been supported in part by funds from the Foster Bequest of the University of Toronto and the National Research Council of Canada. We wish to thank the Connaught Medical Research Laboratories for the insulin and some of the glucagon which we have used. Our major source of glucagon has been Eli Lilly and Company.

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Dr. A. J. DALZELL WARD, medical director of the Central Council for Health Education, said at a recent press conference on the dangers of the common housefly, "Eggs laid last autumn are now hatching out. It takes about 12 days for the egg to hatch and another 12 days to reach maturity. During its brief life the housefly can lay about 900 eggs. Within a couple of months or two generations, therefore, some 800,000 (certainly half a million) flies can come from one fly. In other words one fly can have 800,000 grandchildren." Dr. Ward went on to describe prophylactic measures against the housefly. Obviously the best way to stop this menace to health was to prevent them breeding, he said. The lids of dustbins should be tight and not battered. The bottoms of dustbins should be kept clean and dry, and if possible sprayed with insecticide, preferably one containing D.D.T. It was a good thing to line the bottoms of dustbins with newspaper and renew this whenever they were emptied. As much rubbish as possible should be burned and the remainder, if burning was not possible, kept wrapped and covered until disposed of.

The housefly could and did travel as much as 10 or 12 miles (16–20 km.) from its breeding-place.

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

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The treatment of metastatic breast cancer by surgical castration is the oldest rational method of palliation for this disease (Beatson, 1896). In the series reported by Thomson (1902) and Lett (1905) objective signs of growth regression in pre-menopausal women were observed in 25% of cases. On the other hand, and in sharp contrast, growth regression was limited to a single instance in a series of 25 post-menopausal women.

From 1910 onwards the usefulness of surgical castration was seriously questioned. For over thirty years it was generally discredited, and it was not reinstated until 1942 (Farrow and Adair, 1942) and Beatson's original and cautious claims were confirmed (Adair *et al.*, 1945; Sicard, 1947; Dargent, 1949). Objective remissions in post-menopausal cancer were again shown to be very uncommon.

The therapeutic purpose of surgical castration in pre-menopausal breast cancer is to arrest the progress of the disease by removing the source of ovarian oestrogen production. The palliation induced by this surgical manoeuvre is clearly and intimately related to the regressions which are frequently observed during the "physiological castration" of a natural menopause in breast cancers which, arising during the pre-menopausal period, have already metastasized by the time the patient enters the menopausal phase (Clemmesen, 1948; Hadfield and Holt, 1956).

Laboratory studies of the effectiveness of oophorectomy in abolishing oestrogen production have not been numerous. Bio-assays or biochemical estimations of urinary oestrogens have been reported by Smith and Emerson (1954), Dao (1953), Bulbrook and Greenwood (1957), and McBride (1957), and studies of vaginal cytology were published by Struthers (1956). These investigations revealed that, whilst surgical castration does not abolish the excretion of oestrogens, it does significantly reduce the excretion in pre-menopausal women.

None of the above authors attempted to correlate the immediate and long-term fluctuations in urinary oestrogens with the clinical consequences of the operation. In the present communication this correlation has been attempted.

Material and Methods

All clinical regressions recorded have been based exclusively on observable objective improvement in superficial lesions or in deep lesions visualized by radio-graphy, and all clinical assessments were made without prior knowledge of the biochemical estimations.

Oestrogen-excretion studies were carried out in hospital. Patients were divided into two groups. Those

in the first group had been oophorectomized before this investigation began and no pre-operative oestrogen levels were available. In the second group pre- and post-operative values were determined and the change in oestrogen excretion induced by the operation could be clearly defined.

After discharge all patients attended hospital at monthly intervals, whenever possible bringing a 24-hour specimen of urine. Some were readmitted for several days for clinical assessment and further oestrogen estimations. In a few cases the 24-hour urine specimen was collected from the patient's home. All patients were warned against the use of the several aperients which interfere with oestrogen analysis.

Vaginal smears were taken from the majority of patients and were graded as showing high, moderate, or low oestrogenic activity.

Chemical Methods.—Urinary oestrone, oestradiol-17 β , and oestriol were measured by the method of Brown (1955a) or by the modification proposed by Brown, Bulbrook, and Greenwood (1957a). Results are expressed in $\mu\text{g./24 hours}$ for each oestrogen, or as their sum. Analyses are shown as zero when the amounts of each oestrogen were less than the calculated limits of sensitivity of the method (Brown, Bulbrook, and Greenwood, 1957b). In Case 10, 17-oxosteroids and 17-oxogenic steroids were estimated by the methods of Norymberski, Stubbs, and West (1953) and Gibson and Norymberski (1954), and pregnanediol by the method of Klopfer, Michie, and Brown (1955). The results of both analyses are expressed in mg./24 hours .

1. Clinical Effects and Hormone Excretion After Oophorectomy in Pre-menopausal Women

All patients in this group had a regular menstrual history up to the time of operation. Analyses were carried out on 230 urine specimens from 24 patients in whom progressive metastatic breast cancer had developed after oophorectomy. The mean daily amount of oestrogen was calculated for each patient. These amounts showed no correlation with the time after oophorectomy, and the amounts shown in Table I are the overall means for the 24 patients studied from 1 to 60 months after operation.

TABLE I.—Oestrogen Levels 1 to 60 Months After Oophorectomy in 24 Pre-menopausal Women (230 Analyses)

	Oestrone	Oestradiol-17 β	Oestriol	Total
Arithmetical mean	1.8	0.6	2.9	5.3
Standard deviation	1.0	0.8	2.2	2.6

Results expressed in $\mu\text{g./24 hours}$.

Table I shows that in this group of women the level of oestrogen excretion was much lower than has been found during the normal menstrual cycle.

Four patients treated by oophorectomy for metastatic breast cancer were studied individually at intervals after operation. These patients had shown a regular menstrual history up to the month of operation. In two cases pre-operative oestrogen levels were not estimated, and it was assumed that these were within the normal range (Brown, 1955b). The detailed results are shown in Figs. 1 to 3.

Case Reports

Case 1 (Fig. 1).—This patient was a single woman aged 36. Eleven months after mastectomy, metastases appeared in the ribs, spine, and pelvis; no ovarian or other soft-tissue deposits were detected. Bilateral oophorectomy was carried out. Oestrogen analyses were started two weeks after operation, and up to one month after operation the mean amount of oestrogen was only $2.8 \mu\text{g./24 hours}$. A substantial fall

in oestrogen excretion from the pre-operative level may be assumed to have taken place accompanied by objective

FIG. 1.—Case 1. Excretion of oestrogen after bilateral oophorectomy. In all figures 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 oestriol values. In Figs. 1–6 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.

remission of the disease for four months following operation. Intermittent analyses from two to three months showed an increase in the mean oestrogen level to $3.9 \mu\text{g./24 hours}$. The patient was readmitted to hospital seven months after oophorectomy, and cortisone therapy was initiated, and for a period of three months only trace amounts of oestrogen were detected. In spite of this, from the fourth to the tenth month after oophorectomy there was progressive growth in the skeletal metastases.

Case 2 (Fig. 2).—This patient, aged 53, married, had been menstruating regularly until 10 to 12 months before she was first seen; during that time she had serious menorrhagia.

FIG. 2.—Case 2. Excretion of oestrogen after bilateral oophorectomy.

On admission she had gross pseudo-inflammatory malignant extension in the left breast, hard axillary glands on the same side, and the liver was palpable one fingerbreadth below the costal margin. No skeletal metastases were detected. There were multiple uterine fibromyomata. Hysterectomy and bilateral oophorectomy were performed. Examination of the liver at operation showed multiple metastases in the right lobe. The mean total oestrogen in the first month after oophorectomy was $5.8 \mu\text{g./24 hours}$. Analyses at 7, 10, and 11 months later showed similar values, suggesting that at no time had oestrogen excretion reached zero. Over this period the breast became shrunken and softer, the skin reaction faded, and the nodes decreased in size.

Case 3 (Fig. 3).—This patient was aged 54 and married. Over the previous eight years, and after a left radical mastectomy, the intermittent appearance of clavicular, intercostal, sternal, costal, and supraclavicular swellings had been treated by deep x rays. When admitted to hospital she had pelvic bone metastases and a left pleural effusion. Admission interrupted an otherwise regular history of menstruation. The vaginal smear indicated high oestrogenic activity. Urinary excretion of oestrogen was irregular but showed a normal excretion pattern of the individual oestrogens and a total amount within the normal range (Brown, 1955b). 17-oxosteroid excretion was normal and relatively constant at 3.4 mg./24 hours . Operation revealed metastatic deposits in both ovaries. Oophorectomy produced an arrest in growth but no objective regression for a period of three

months, associated with a reduction in mean oestrogen excretion from 15.5 to 3.9 $\mu\text{g.}/24$ hours, and a change in the appearance of the vaginal smear from high to moderate activity in the first two months after operation. The pre-operative lesions were virtually unchanged over the three-

FIG. 3.—Case 3. Excretion of oestrogen before and after bilateral oophorectomy.

months period and a return to active growth and the reappearance of other skeletal secondaries was preceded by a slight rise in oestrogen excretion (5.3 $\mu\text{g.}/24$ hours) and a return of the vaginal smear to one of high oestrogen activity. Intermittent analyses from the fourth to the sixth month after operation showed an irregular excretion around a mean value of 3.2 $\mu\text{g.}/24$ hours. The patient died seven months after operation. Post-mortem examination revealed diffuse carcinomatosis; secondary deposits were found in the adrenal glands.

Case 4.—This patient, aged 44, married, had a history of recurrence of growth after a previous mastectomy similar to that described in Case 3. Oestrogen excretion before operation showed a similar picture—irregular excretion but a normal pattern and total amount; the mean pre-operative level was 14.4 $\mu\text{g.}/24$ hours. Clinically, oophorectomy had no effect, but regression of the lesions was obtained by irradiation from one to three months after operation. Oestrogen levels were investigated only at the fourth month. At this time oestrogen was still present, although in amounts (3.3 $\mu\text{g.}/24$ hours) well below the mean pre-operative level. The patient died seven months after operation. Post-mortem examination showed diffuse carcinomatosis.

Summary of Findings in Pre-menopausal Group

The mean excretion of Cases 3 and 4 before operation was about 15 $\mu\text{g.}/24$ hours. Similar figures have been given for pre-menopausal women with breast cancer (Birke *et al.*, 1958) and for normal women (Brown, 1955b). The results shown in Table I, and Figs. 1 to 3, afford further evidence that oophorectomy in pre-menopausal women removes a major source of oestrogen production. Although well marked in Cases 3 and 4, the reduction in oestrogen excretion was not accompanied by objective remission of the disease.

The range and mean levels of oestrogen excreted after oophorectomy demonstrate that adrenal secretion of oestrogen is always detectable after operation and can vary within wide limits. The results obtained in the first few days after operation (Case 3) suggest that the adrenal glands contribute to excretion before oophorectomy, and this component may be temporarily increased by operative stress.

The finding that adrenal secretion of oestrogen is usual after oophorectomy would afford at least a rational explanation for the clinical failure of the operations in Cases 3 and 4, but remission of the disease was obtained in Cases 1 and 2, although oestrogen was always detectable in the urine. The levels of oestrogen in the latter cases do not differ from the levels found in the group with progressive disease (Table I).

2. Clinical Effects and Hormone Excretion After Oophorectomy in Menopausal Women

For the purpose of this paper we have defined as "menopausal" those women who last menstruated less than a year before oophorectomy. A group of six patients who had been oophorectomized for metastatic breast cancer during

the menopause was investigated. Oestrogen studies after oophorectomy were made at a time when the disease had recurred, from 1 to 24 months after operation, in these patients. Table II shows the mean oestrogen levels based upon the analysis of 50 urine specimens from the six patients. The amounts and pattern of oestrogen excreted do not differ from that found in the pre-menopausal group (Table I).

TABLE II.—Oestrogen Levels 1 to 60 Months After Oophorectomy in Six Menopausal Women (50 Analyses)

	Oestrone	Oestradiol- 17β	Oestriol	Total
Arithmetical mean ..	1.8	0.4	3.9	6.1
Standard deviation ..	1.5	0.5	5.3	6.4

Results expressed in $\mu\text{g.}/24$ hours.

More detailed studies were made on four menopausal patients with metastatic breast cancer.

Case 5 (Fig. 4).—This patient, aged 45, married, had a previous history of mastectomy, with the later appearance

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

FIG. 5.—Case 6. Excretion of oestrogen before and after bilateral oophorectomy.

of supraclavicular nodes. These and subsequent pelvic bone deposits were treated by deep x-ray therapy. Periods were regular until nine weeks prior to oophorectomy but had ceased at this time incidental to the deep x-ray therapy. Excretion of oestrogen was very low, but oophorectomy occasioned a transient though pronounced rise in excretion. An objective regression of five months' duration followed oophorectomy. No oestrogen could be detected three months after operation. The disease progressed from the sixth month until death, 13 months after operation. Oestrogen excretion during this period had returned to a mean value of 5.2 $\mu\text{g.}/24$ hours, above the pre-operative level of 1.9 $\mu\text{g.}/24$ hours.

Case 6 (Fig. 5).—This patient, aged 55, married, had a six-months history of a lump in the breast with involvement of the axilla. Treatment by deep x rays to the breast and axilla was started. Menstruation had been regular until six months before operation. Just before operation the

vaginal smear showed moderate to high oestrogen activity, but the total amount of oestrogen was low. The immediate effect of oophorectomy was difficult to evaluate, since deep x-ray treatment was continued. A very low level was found in the first month after operation. Clinically some subjective improvement was noted for the first post-operative month, but by the third month deep x-ray treatment to the breast and axilla was resumed. Subsequent progression of the disease, with the appearance of new lesions, was noted over a period from the fifth to the seventeenth month after operation. Oestrogen excretion had increased by the tenth month, and a further very marked rise was shown in the seventeenth month, a few days before death.

Case 7.—This patient was single, aged 42. Fifteen months after mastectomy and deep x-ray treatment for carcinoma of the right breast she developed a pleural effusion and metastases in the spine, ribs, and pelvis. Pre-operative oestrogen (2.6 $\mu\text{g.}/24$ hours) and 17-oxosteroid excretion (1 mg./24 hours) were low. At operation both ovaries contained secondary deposits. Both oestrogen and 17-oxosteroid excretion were raised above the pre-operative levels in the month after oophorectomy (7.6 $\mu\text{g.}/24$ hours and 5 mg./24 hours respectively). The progress of the disease was not affected by operation. Some palliation was obtained with deep x-ray treatment, but the patient died four months after oophorectomy with widespread pleural and pulmonary metastases and skeletal deposits. At post-mortem examination deposits were found in both adrenal glands.

Case 8.—This patient, aged 51, married, had a seven-months history, before oophorectomy, of an inoperable carcinoma of the left breast with gross skin and axillary node involvement. Improvement had been obtained by deep x-ray treatment and the disease appeared to be responding. Four months prior to operation vaginal smears showed high oestrogenic activity. At operation oestrogen excretion was not high (3.6 $\mu\text{g.}/24$ hours) and an atypical fall to zero was obtained up to the time of discharge, the 17-oxosteroid excretion being unchanged by operation. An objective regression lasting for three years followed oophorectomy, but as it has been impossible to carry out further investigations it is not known whether oestrogen secretion has returned or not.

Summary of Findings in the Menopausal Group

The oestrogen levels of the individual patients before and after operation do not differ from those found in the group of patients studied after operation (Table II). The pre-operative levels are low compared with those found in pre-menopausal women, and suggest that in the menopausal cases an ovarian contribution was absent before operation. The immediate effects of operation on oestrogen excretion in this small series show three variations: unchanged, increased, and decreased excretion.

The immediate effects of oophorectomy on oestrogen secretion would appear to be determined by the degree of operative stress and the individual reaction to this. In the two cases followed for some time after operation the immediate effects were not maintained. In Case 5 the excretion fell to zero over a period of remission, and rose with the progression of the disease; in Case 6 the oestrogen excretion, unchanged by operation, rose as the disease progressed.

The four cases show a clear association between the effects of oophorectomy on oestrogen excretion and the clinical state. The operation was not effective in two cases showing an increased or unchanged excretion, but objective regressions were produced in the two cases in which oestrogen excretion fell to zero. In one of the latter, oestrogen excretion returned when the patient relapsed.

3. Clinical Effects and Hormone Excretion After Oophorectomy in Post-menopausal Women

We have defined as "post-menopausal" those women who had not menstruated for at least one year before

TABLE III.—Oestrogen Levels 2 to 8 Years after the Menopause in 16 Post-menopausal Women (81 Analyses)

	Oestrone	Oestradiol-17 β	Oestriol	Total
Arithmetical mean	1.8	0.9	2.4	5.0
Standard deviation	1.3	1.3	2.1	2.6

Results expressed in $\mu\text{g.}/24$ hours.

TABLE IV.—Oestrogen Levels 2 to 36 Months After Oophorectomy in Six Post-menopausal Women (31 Analyses)

	Oestrone	Oestradiol-17 β	Oestriol	Total
Arithmetical mean	1.8	0.9	3.5	6.3
Standard deviation	1.0	0.6	1.9	2.7

Results expressed in $\mu\text{g.}/24$ hours.

FIG. 6.—Case 9. Excretion of oestrogen before and after bilateral oophorectomy.

oophorectomy. A comparison of the oestrogen excretion levels of a group of post-menopausal women with metastatic breast cancer with the readings from a similar group after oophorectomy shows that the results are the same in the two groups (Tables III and IV) and suggest that oophorectomy has no effect on oestrogen excretion.

Four cases studied before and after oophorectomy conform to this general pattern, and in these no regression of the disease was obtained. In addition, three of the four cases showed an increased excretion of oestrogen within the first weeks after operation. Case 9 illustrates the general findings in this group.

Case 9 (Fig. 6).—The patient, aged 52, married, had a one year's history of inoperable breast cancer treated by deep x rays, and subsequently by oophorectomy for skeletal metastases, with no effect. The disease slowly progressed, and by the ninth month after opera-

FIG. 7.—Case 10. Excretion of steroids before and after mastectomy. Each vertical column gives the mean of a duplicate determination for oestrogen, pregnanediol, 17-oxosteroid, and 17-oxogenic steroid on a 24-hours specimen of urine.

tion the breast had ulcerated and the bone metastases had spread. The patient died 11 months after operation. The immediate effects of operation are shown in Fig. 6. The mean pre-operative level was 9.2 $\mu\text{g.}/24$ hours, and in the first two weeks there was a marked adrenal reaction to operation, the mean level being 12.7 $\mu\text{g.}/24$ hours.

A more detailed study of operative stress is shown in Case 10.

Case 10 (Fig. 7).—The patient, aged 56, married, was post-menopausal, had an operable breast cancer, and was treated by mastectomy only. The rise in oestrogen excretion was not marked and took place from the first to the fourth day after operation before reaching pre-operative levels. The increase in 17-oxosteroid, 17-oxogenic steroid, and pregnanediol excretion was more marked, and occurred on the first and second days after operation.

Summary of Findings in the Post-menopausal Group

As with the group of menopausal women, the immediate effect of oophorectomy may be an increase in oestrogen excretion due to operative stress. The overall effect of oophorectomy in the post-menopausal women is that both the clinical course of the disease and the oestrogen levels remain unaltered.

Discussion

The levels of urinary oestrogen found after oophorectomy in pre-menopausal, menopausal, and post-menopausal women with metastatic breast cancer are similar in amount and pattern to those of normal menopausal and post-menopausal women. It is only in pre-menopausal women that a post-operative fall invariably takes place. In all three groups there are considerable variations in the total amount of oestrogen excreted after operation, and the quantity varies from one patient to another and in each patient at different times. In many instances the levels approach those found in normal menstruating women. On the other hand, oestrogen excretion is rarely recorded as being below 1 to 1.5 $\mu\text{g.}/24$ hours, the arbitrary limit imposed by the sensitivity of the chemical method used.

The failure of surgical castration to reduce oestrogen excretion in menopausal and post-menopausal women is probably related to variations in the relative amounts of oestrogen contributed by the ovary on the one hand and the adrenal on the other. No fall in oestrogen could be expected if the ovarian contribution were negligible, whilst a post-operative suppression of ovarian oestrogen production could be offset by an increase of adrenal oestrogen production, such adrenal overactivity being a possible result of operative stress. This interpretation of our clinical and biochemical observations in menopausal and post-menopausal women affords some justification for further endocrine ablation as the subsequent treatment of choice. Adrenalectomy would be expected to accomplish both a steep fall in oestrogen excretion and a reduction below a critical level, which in all probability varies from patient to patient.

The removal of the pre-menopausal ovaries, although reducing oestrogen excretion, is not always accompanied by regression of the disease. There are several possible explanations for this observation, but no definite conclusions can be drawn from the data presented in this paper. For example, the beneficial effects of oophorectomy in some pre-menopausal women may depend upon the extent of the post-operative fall in oestrogen production. This is unlikely to be constant in all patients submitted to oophorectomy, since it depends upon the relative contributions of the ovaries and adrenal glands pre-operatively, the stressing effect of the operation on adrenal secretion, and the "resting" level of adrenal oestrogen production. Each of these factors is known to vary widely from patient to patient (Brown, 1958; Birke *et al.*, 1958; this paper), and this would

provide an adequate basis for the variation to be expected in the extent of the fall in oestrogen production after oophorectomy.

Alternatively, the clinical success of oophorectomy may depend upon the reduction of circulating oestrogen below a critical level irrespective of the pre-operative level. If this be attained regression might follow. On the other hand, such a period of growth remission could be interrupted by a period of progressive growth if adrenal oestrogen production were increased by a sustained episode of traumatic stress. The well-attested variation in the capacity of the adrenal glands to take over oestrogen production after surgical castration has already been emphasized and the absence of oestrogen in two cases in objective remission may well be significant examples of this phenomenon.

For this discussion we have used the simple example of oestrogen reduction. It must be appreciated that the effects of oophorectomy, like the effects from the natural menopause, are not those of simple oestrogen removal or reduction, but involve a complex of changes which result in a gross disturbance of both adrenal and pituitary function in addition. It is probable that tumour regression is not related to simple changes in oestrogen, but is related to the whole complex of changes by alteration in oestrogen, progesterone, and pituitary hormone variation.

Summary

The effects of bilateral oophorectomy upon the clinical state and oestrogen excretion have been studied in patients with metastatic breast cancer.

Objective remission in pre-menopausal women after oophorectomy was not invariable, despite a fall in oestrogen excretion. Possible reasons for this are presented.

Objective remission in menopausal and post-menopausal women appeared to be unlikely unless the ovarian contribution of oestrogen was significant and adrenal secretion of oestrogen unaffected by operation.

Oestrogen derived from the adrenal glands appears to be present in all patients after oophorectomy. The removal of this source of production by further endocrine surgery appears to be indicated when oophorectomy fails to arrest the progress of the disease.

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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