cases. There was no clear association between length of history and gland involvement.

The various methods of treatment are discussed. Simple surgery was undertaken in 229 cases, more than half of which were treated by simple excision of the tumour. Radical mastectomy was done in 338 cases, and the modified radical operation in 167. Radium treatment without surgery was used in 149 cases, and x rays alone in 114. Forty-seven cases were not treated. Of the cases treated surgically, about two-thirds were also given irradiation. This type of treatment became more frequent towards the end of the period, and at the same time x rays tended to replace radium, particularly in combination with simple surgery.

Five- and ten-year survival rates, adjusted for variations in age distribution, are calculated for different clinical stages and treatment groups. The adjusted rates for all treated cases in stage I were as follows: five-year, 72%; ten-year, 51%. The corresponding figures for stage II were: 39% and 26%. The rates for the individual treatment groups showed no appreciable departure from these figures despite the fact that simple surgery consisted merely of local excision in more than half the cases; nor did the addition of irradiation affect the rates, although it is possible that selection of cases may have concealed some of the benefits of radiotherapy.

Attention is drawn to the lower survival rates in the cases assessed clinically to be in stage II but with axillary glands pathologically free, compared with stage I cases with glands involved.

The mortality of radical mastectomy was 1.2%. Oedema of the arm occurred after radical surgery in 14% of cases, compared with 5% after simple surgery, and was almost twice as frequent when the radical wound gave rise to complications as in those with primary healing.

There seemed to be fewer local recurrences following radical surgery than other types of surgery, but the addition of radiotherapy appeared to make no difference in this respect.

It was concluded from a general discussion that where efficient radiotherapy is available radical mastectomy should be abandoned in favour of conservative surgery.

We wish to express our gratitude to Mr. Reginald Vick, Mr. Geoffrey Keynes, Sir James Paterson-Ross, and the other members of the staff of St. Bartholomew's Hospital who allowed us to undertake a study of patients who were under their care. Our thanks are also due to Dr. Christine Abernethy and Mrs. Perkins, who have both contributed to the completeness of the follow-up records, and to the staffs of the follow-up and statistics departments, on whom fell much of the routine work.

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TREATMENT BY OESTROGENS OF PULMONARY METASTASES FROM BREAST CANCER

BY

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In a previous paper, based on treatment of 152 cases of advanced breast carcinoma by oestrogens, one of us has commented on the encouraging results in cases of pulmonary metastasis. It was recorded that out of 25 cases of pleural or lung metastases treated by oestrogens there were nine survivals for longer than 12 months (Stoll, 1950). In the majority of these cases, also, there was radiological evidence of regression of these metastases. This achievement is remarkable in view of the average survival of only about three months in similar untreated cases. The series has now been expanded to 61 cases treated at the London Hospital Radiotherapy Department between 1943 and 1950. In addition, the results are compared with a series of 66 cases of pleural and lung metastases seen during the same period but not treated by oestrogens. All cases were supervised by one or other of us.

The background of the cases must first be examined. The number of cases of breast carcinoma recorded with pleural or lung metastases from 1943 to 1950 was 159, and the number of cases with pleural or lung metastases, verified radiographically, was 127. Of these latter cases, oestrogens were prescribed in 61 and not prescribed in 66. The selection of cases for hormone administration was statistically random but not controlled. When the cases came to be analysed it was found that the proportion of cases of a younger age group was considerably higher in the untreated than in the treated group (Table VI). That this distribution did not influence the results is seen in the same table, where for each group the age of the patient was found to exert no influence on the length of survival. This fact is further commented on later.

Length of Survival after Oestrogen Treatment of Pulmonary Metastases

TABLE I.—Months of Survival in Treated and Untreated Cases

Months Survival	Cases of Pleural Metastasis		Cases of Lung Metastasis		Total	
	T.	U.	T.	U.	Treated	Untreated
1-3	17	31	6	12	23 (5 still alive)	43 (all dead)
4-6	9	10	3	4	12 (4 " ")	14 (" ")
7-11	5	3	2	1	7 (2 " ")	4 (" ")
12+	9	4	10	1	19 (9 " ")	5 (" ")
Total ..	40	48	21	18	61	66

TABLE II.—Comparative Percentage Survival in Treated and Untreated Cases

	Treated Group	Untreated Group
Died within 3 months ..	29.5%	65%
" 4-11 months ..	21.5%	27.5%
Survival over 12 months ..	31%	7.5%
Still alive, 1-11 months ..	18%	—
	100%	100%

The survivals in months following the prescription of oestrogens are shown in Table I. In all except eight cases the treatment was begun within one month of the diagnosis of pleural or lung metastases. (In these eight cases the patient had survived varying periods from 3 to 12 months before the institution of oestrogen therapy, and in three of these cases the patients survived over 12 months more and are noted as such.)

The survivals in months following the diagnosis in the untreated cases are also shown for comparison in Table I, and the percentage survivals are compared in Table II. From this last table it is seen that 19 out of 61, or 31%, of the treated group survived over 12 months, compared with only 5 out of 66, or 7.5%, in the untreated group. In addition, a further 18% are still alive at periods varying from 1 to 11 months after oestrogen therapy, a proportion of whom may well survive over 12 months. There is, therefore, definite evidence of prolongation of life by the use of oestrogens in these cases. The difference between the proportions surviving over 12 months is greater than the spread to be expected using 95% confidence limits, and is thus statistically significant (Boag, 1948; Wood and Boag, 1950).

Mere survival over 12 months is unusual enough, in cases of lung metastasis, to the clinician who sees large

numbers of them. In addition, however, it is of interest to assess the final duration of life in these cases.

Fig. 1 shows the survivors month by month in the untreated group and Fig. 2 the survivals in the treated group. It is seen that in the untreated group 57 out of 66 patients died within six months, but in the treated group only 26 out of 52 had died in that period. (A further nine patients were still alive after having been followed up for six months or less.) The average length of survival for the untreated cases was 3.7 months, which is in accord with most clinicians' experience. Finally, it is noted that, whereas in the untreated group none out of 66 cases survived over 18 months, in the treated group 11 out of 61 survived over 18 months, five over 24 months, and three over 36 months. It is thus obvious that the administration of oestrogens leads merely to temporary control of the disease rather than to cure.

Regression of Pulmonary Metastases following Oestrogens

Apart from prolongation of survival, it is of interest to note the behaviour of pulmonary metastases following oestrogens. As shown in Table III, the cases surviving 12

TABLE III.—Regression of Pulmonary Metastases Following Oestrogens

Lesion	Total Cases	Cases Surviving 12 Months	Cases with Radiographic Regression
Lung metastases ..	21	10	7
Pleural ..	40	9	9
Total ..	61	19 (31%)	16 (26%)

FIG. 1.—Numbers surviving month by month after diagnosis of metastasis. Untreated group, 66 cases.

FIG. 2.—Numbers surviving month by month after institution of oestrogens for metastasis; 61 cases

months or more after oestrogen therapy include 10 out of 21 cases of lung metastases and 9 out of 40 cases of pleural metastases. In the former group 7 out of 10, and in the latter group 9 out of 9, showed radiographic evidence of regression of metastases. Such regression develops after two to four months in the majority, but in some cases there was evidence of new lung or pleural metastases after 12 months. There was evidence of regression of pulmonary metastases also in a further three patients who are still alive but who have not completed 12 months' survival. The total of cases showing radiographic evidence of regression is thus 16 out of 61 cases (26%). When we compare the untreated group we find that, although 5 cases out of 66 survived over 12 months, in no case was there evidence of regression of pulmonary metastases.

Survival in Relation to Duration and Dose of Oestrogen

The dose prescribed was, in the main, either 2 or 20 mg. of stilboestrol daily, according to the random choice method advocated by the Oestrogen Research Committee set up by the British Empire Cancer Campaign and Royal Society of Medicine.

Table IV shows that of the 39 patients who had taken the drug for three months or more, 57% survived seven months or longer. Of the 22 taking the drug for two months or less, 18% survived over seven months. It would appear from these figures that with more prolonged administration of oestrogens the results are better. In spite of this it must be recalled that it was previously noted that regression of

TABLE IV.—*Duration of Oestrogen Administered in Relation to Survival*

Duration of Oestrogen	Total Cases	Cases Surviving over 7 Months
Over 3 months	39	22 (57%)
Less than 3 months	22	4 (18%)
Total	61	26

pleural effusion occurred in some cases after administration of oestrogens for two months. It must therefore be assumed that two months is adequate to establish a reaction capable of controlling the disease. It might be relevant to recall at this point that recognizable regression of soft-tissue metastases in breast carcinoma usually occurs after three months' administration of oestrogens (Stoll, 1950).

With regard to the optimal dose of oestrogen, it is seen from Table V that of the 26 cases receiving 2 mg. daily, 35% survived over seven months. This compares with 35 cases receiving 20 mg. daily, of whom 49% survived over

TABLE V.—*Dose of Oestrogen in Relation to Survival*

Dose of Oestrogen	Total Cases	Cases Surviving over 7 Months
2 mg. daily	26	9 (35%)
20 " "	35	17 (49%)
Total	61	26

seven months. The difference between the two groups is not significant, suggesting that the lower dose is sufficient to exert the maximal possible effect. This is in agreement with the effect of oestrogens on soft-tissue metastasis noted in the previous paper, but does not agree with some other authorities. Walpole and Paterson (1949) noted a better result with 20 mg. of dienestrol or stilboestrol daily than with 1-2 mg. daily. It must be noted that the oestrogenic potency of dienestrol is one-fifth that of stilboestrol, and thus the smaller dose of dienestrol would be equivalent to about 0.25 mg. of stilboestrol daily—a dose which may be quite insufficient.

Effect on Concomitant Soft-tissue Metastases

In 29 of the treated cases there were signs of active growth involving the soft tissues—that is, skin or glands. In only eight of these cases were there signs of regression in these metastases, but five of these survived over 12 months in spite of pulmonary metastases. There is therefore some degree of correlation between the response of the two types of metastasis to oestrogens.

Survival in Relation to Age Group

As noted before, the proportion of cases of a younger age group was considerably higher in the untreated group than in the treated group. In order to assess what possible bias effect this might have on the comparison of the two series, Table VI was planned.

It is seen from Table VI that in the treated group the seven-months survivals in the under 59 and over 60 group

TABLE VI.—*Survival in Relation to Age Group; Treated and Untreated Cases*

Months Survival	Under 59 Group		Over 60 Group		Total	
	T.	U.	T.	U.	T.	U.
1-3	7	27	16	15	23	42
4-6	7	12	5	1	12	13
7-11	5	3	2	1	7	4
12+	6	3	13	2	19	5
Total ..	25	45	36	19	61	64*

* Plus two cases, age unknown.

are 44% and 42% respectively. In the untreated group the seven-months survivals are 13% and 16% respectively for the two age groups. There is thus no obvious difference between the age groups in the expectation of life in either treated or untreated groups, and therefore the inequality of the age distribution does not vitiate the value of the control series.

It is of interest to note that in the case of soft-tissue metastases there is generally agreed to be a notable difference between the under 60 and the over 60 age groups in their response to oestrogens. The Royal Society of Medicine symposium in 1944 quoted 14% and 40% regression respectively.

Possible Prophylactic Effect of Oestrogens

In spite of the proved value of oestrogens in the treatment of pulmonary metastases from breast carcinoma, there is no evidence that they exert any protective effect against the development of such metastases even during their administration.

In the period under review 147 patients for whom oestrogens were prescribed for breast carcinoma showed no evidence of pulmonary metastases at the time of prescription. In 41 of these pulmonary metastases developed at a later date (in 15 cases while the patient was taking oestrogens), in 13 within three months of stopping oestrogens, and in a further 13 more than three months after stopping oestrogens. While no prophylactic effect is shown by these figures, there is no suggestion that oestrogens can be incriminated as precipitating pulmonary metastases.

Discussion

Relevant to the regression of pleural effusions in these cases, associated with long-term survivals, it would be useful to discuss the other possible causes, apart from metastases, which might lead to such effusions. The main possibilities are (a) idiopathic effusion—usually tuberculous; (b) effusion as a reaction to irradiation of the thorax; and (c) hydrothorax as a complication of cardiac or renal disease. All these may lead to an effusion which can regress spontaneously.

The differential diagnosis of a malignant effusion depends on certain features. The effusion is said to be blood-stained, but this is not always so, because the fluid may be a transudate following pressure on the pulmonary veins by metastatic mediastinal glands. The presence of neoplastic cells in the fluid is diagnostic, but notoriously difficult to establish. Associated haemoptysis is occasionally noted, and indicates underlying lung involvement; and, indeed, deposits in the lung may often be shown by a radiograph to coexist, or they may develop later. Involvement of the opposite side in the case of unilateral lesions is a more or less inevitable result. The development of spontaneous hydropneumothorax (as seen in two cases in this series) suggests the rupture of a subpleural metastasis in the lungs.

The clinical picture of the patient with malignant effusion is usually typical. A sudden onset of dyspnoea is frequently associated with a very small effusion, the degree of dyspnoea often being apparently out of proportion to the size of the effusion. A malar flush is common and may be due to cyanosis, but is often associated with a degree of pyrexia. Essentially, however, the diagnosis of malignant effusion is presumptive upon the history of breast carcinoma and must be regarded as such unless proved otherwise.

The possibility of pleural effusion resulting from radiation changes must be considered. Although depending on the technique used for irradiation of breast carcinoma, radiation changes in the lungs are not infrequent. As a rule they develop six to nine months after a course of irradiation and usually lead to lung fibrosis, which may persist unchanged for years. Occasionally a transient patch of pneumonitis may develop, mostly soon after treatment. The site of the changes is typical for the irradiation technique used and

TABLE VII.—*Site of Effusion in Relation to Site of Primary Breast Tumour*

Site	Cases in Untreated Group	Cases in Treated Group	Total
Ipsilateral	36	33	69 (80%)
Contralateral	8	4	12 (14%)
Bilateral	3	2	5 (6%)
Total	47	39	86

In two cases the side was unspecified.

TABLE VIII.—*Survival in Relation to Date of Previous Irradiation in the Case of Ipsilateral Effusions*

Months Survival	Months since Last Irradiation of Same Side of Chest				Total
	1-11	12-23	24+	No Irradiation	
1-3	15	8	4	8	35
4-6	7	4	1	5	17
7-11	3	1	—	1	5
12+	1	3	3	5	12
Total ..	26	16	8	19	69

corresponds to the junction of the supraclavicular and tangential fields in the cases treated in the London Hospital radiotherapy department. Pleural effusion is almost never associated with the lung changes, although in 2 out of the 68 cases of effusion in this series there were signs of apical lung fibrosis antedating the development of the effusion by some months.

In an attempt to clarify any relationship between the pleural effusion and the antecedent irradiation, Tables VII and VIII were planned.

Table VII shows that of the 86 cases in which the primary site of effusion is specified, in 80% the site was ipsilateral to the original breast lesion, in 14% contralateral, and in 6% bilateral. When only 19 previously non-irradiated cases are considered the proportion of ipsilateral effusion is 74%, suggesting that ipsilateral effusion is the common result of malignant metastases.

Table VIII shows that 26 out of the 69 cases of ipsilateral effusion developed within 11 months of irradiation being given to that side of the chest. If pleural effusion is a complication of irradiation one might suspect this group of cases, and, if so, it should provide the cases of regression and long survival. In actual fact, 22 out of these 26 patients did not survive six months, and only one survived over 12 months.

We consider that the most conclusive evidence that the effusions were malignant in this series is the death within 17 months of all the patients in the untreated control series.

A final observation is presented on the radiographic appearance of lung metastases from breast carcinoma. Of the 39 cases in the series, 23 presented with a single rounded opacity or multiple mottling in one or both lung fields; nine with lymphangitis carcinomatosa with reticulation throughout the lung fields and increase in the size of the hilar shadow; five with hilar gland enlargement alone; and two with a localized area of collapsed lung with later evidence of further lung involvement.

Regression of lung metastases from breast carcinoma by the use of oestrogens has been quoted by Paterson (1950). There was regression in two out of seven cases.

Case Histories

There were 10 patients with lung metastasis (apart from the nine cases of pleural metastasis) who survived over 12 months. Their case histories are appended.

Case 1.—Aged 67; post-menopausal. October, 1944, history of left mastectomy 23 years before. Patient attended with carcinoma of the right breast. November, 1944, deep x-ray treatment of right breast. November, 1945, radiograph showed multiple rounded shadows in the left lung field; stilboestrol, 5 mg. q.i.d., prescribed. April, 1946, lung metastases fading and stilboestrol stopped. January, 1947, recurrence of shadowing and also left pleural effusion; stilboestrol restarted and continued. June, 1947, increase in effusion and spread of left lung metastases. October, 1947, patient died, 23 months after original lung metastases.

Case 2.—Aged 66; post-menopausal. July, 1948, attended with ulcerated carcinoma of right breast and fixed axillary glands. October, 1948, radiograph showed multiple rounded shadows in both lung fields (Fig. 3); stilboestrol, 0.5 mg. q.i.d., prescribed and continued. January, 1950, deep x-ray treatment of right breast in view of response of lung metastases. July, 1950, partial regression of lung metastases (Fig. 4). February, 1951, patient alive and slightly dyspnoeic on exertion, 28 months after the original lung metastases.

FIG. 3.

FIG. 4.

FIG. 3.—Case 2. Radiograph taken on October 1, 1948, showing multiple rounded shadows in both lung fields. FIG. 4.—Case 2. Radiograph on July 12, 1950, showing partial regression of lung metastases.

FIG. 5.

FIG. 6.

FIG. 5.—Case 7. Radiograph on February 28, 1950, showing multiple rounded opacities in mid-zones of both lungs. FIG. 6.—Case 7. Radiograph on February 2, 1951, showing partial resolution of lung opacities.

Case 3.—Aged 53; post-menopausal. April, 1945, right mastectomy followed by deep x-ray treatment for breast carcinoma. January, 1947, right supraclavicular metastases treated by deep x rays. October, 1947, radiograph showed prominence of both hilar shadows and reticulation in the lung fields, diagnosed as lymphangitis carcinomatosa. January, 1948, stilboestrol, 5 mg. q.i.d., prescribed and continued; deep x-ray treatment given to pelvic metastases. August, 1949, decrease in size of hilar shadows, and lung fields appear clearer, although right diaphragm now raised. January, 1950, patient died, 27 months after the original lung metastases.

Case 4.—Aged 52. October, 1945, right mastectomy for breast carcinoma. January, 1946, radiograph showed rounded shadow at right costophrenic angle; stilboestrol, 0.5 mg., prescribed and continued for 14 months. April, 1946, deep x-ray treatment to mass on right chest wall. March, 1947, deep x-ray treatment to left supraclavicular metastases. July, 1947, shadowing at right base unchanged. In addition there was a right interlobar and left basal effusion, and generalized increase in lung markings. September, 1947, patient died, 19 months after the original lung metastases.

Case 5.—Aged 75, post-menopausal. December, 1945, attended with carcinoma right breast. January, 1946, deep x-ray treatment to right breast and glandular areas. June, 1947, radiograph showed bilateral hilar gland enlargement; stilboestrol, 5 mg. q.i.d., prescribed and continued. February, 1951, radiograph showed clearing of hilar shadows; patient alive 44 months after original mediastinal metastases.

Case 6.—Aged 65; post-menopausal. March, 1948, right mastectomy for breast carcinoma. August, 1948, post-operative deep x-ray treatment to right chest wall and glandular areas. December, 1949, radiograph showed multiple rounded opacities in both lung fields. January, 1950, deep x-ray treatment to right supraclavicular metastases. December, 1950, stilboestrol, 0.5 mg. q.i.d., prescribed and continued. March, 1951, radiograph showed no change in lung shadows. May, 1951, patient alive 17 months after original lung metastases.

Case 7.—Aged 71; post-menopausal. July, 1947, right mastectomy for breast carcinoma. November, 1947, post-operative deep x-ray treatment to right chest wall and glandular areas. February, 1950, radiograph showed multiple rounded opacities in mid-zones of both lungs (Fig. 5); stilboestrol, 5 mg. q.i.d., prescribed and continued for seven months. February, 1951, radiograph showed partial resolution of lung opacities (Fig. 6). April, 1951, patient alive 14 months after original lung metastases.

Case 8.—Aged 59; post-menopausal. September, 1949, attended with carcinoma right breast and fixed axillary glands; radiograph showed rounded multiple opacities in both lung fields. November, 1949, deep x-ray treatment to right breast. February, 1950, stilboestrol, 0.5 mg. q.i.d., prescribed and continued. April, 1951, radiograph showed partial resolution of lung opacities. May, 1951, patient alive 20 months after original lung metastases.

Case 9.—Aged 66; post-menopausal. August, 1949, attended with carcinoma left breast and fixed axillary glands; stilboestrol, 5 mg. q.i.d., prescribed and continued. October, 1949, deep x-ray treatment to left breast and glandular areas. February, 1950, radiograph showed bilateral hilar gland enlargement with extension into lung-fields; diagnosed as lymphangitis carcinomatosa. June, 1950, shadowing on right side cleared after four months. October, 1950, testosterone, 800 mg. monthly, prescribed for ulceration of left breast which was not responding to stilboestrol. April, 1951, radiograph showed decrease in left lung infiltration; breast ulceration regressing on testosterone. May, 1951, patient alive 15 months after original lung infiltration.

Case 10.—Aged 47; cyclical. October, 1943, deep x-ray treatment to carcinoma right breast with multiple skin nodules. December, 1944, radiograph showed opacity in

right lower zone, ? nature; this increased slowly in size. July, 1946, stilboestrol, 5 mg. q.i.d., prescribed and continued for 13 months. December, 1947, radiograph showed no new opacities; stilboestrol stopped. June, 1948, radiograph showed multiple opacities in right mid zone, left basal effusion, and radial shadowing suggesting lymphogenous spread; stilboestrol restarted. November, 1948, patient died, 47 months after original lung shadowing.

Summary

A report is made on 61 cases of pleural or lung metastasis secondary to breast carcinoma treated by oestrogens. A series of 66 similar cases which were not treated is used for comparison.

In the treated group 31% of cases survived over 12 months, as compared with only 7.5% in the untreated group. In the treated group 26% of cases showed regression of pulmonary lesions, compared with 0% in the untreated group.

The possibility of a non-malignant aetiology in the cases with long survival is discussed.

The effect of oestrogens in these cases is essentially temporary, and no prophylactic effect against the development of pulmonary metastases can be shown.

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TEN YEARS' CLINICAL EXPERIENCE OF MODIFIED LEUCOTOMY OPERATIONS*

BY

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It is over 10 years since some of us, evacuated to Sutton Emergency Hospital from the Maudsley Hospital during the last war, decided to approach Mr. Wylie McKissock, of St. George's Hospital, about attempting modifications of the standard leucotomy operation, then being used in America by Freeman and Watts, so as to investigate its possibilities in the treatment of selected neuroses. I had already seen some results of the early full standard leucotomy in Washington in 1938, and it was obvious then that this operation would come to be used in the neuroses, but cuts would have to be modified, if possible, to try to prevent some of the sequelae seen in these patients. A little later on Mr. G. Knight also offered to help in such work at the West End Hospital for Nervous Diseases.

Experimental Work

Our earliest experiments were not as satisfactory as one would have desired. We were able to do some at our own hospital, but in those days permission to perform such operations had to go through varied L.C.C. and E.M.S. administrative channels, and viewpoints could be so conflicting that varied makeshifts had often to be employed to enable them to take place at all, even on the most carefully selected and studied patients.

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