1958). In women also, the death-rate from lung cancer has increased considerably. The extensive statistical and epidemiological evidence associating tobacco smoking and lung cancer is clear for all to study. Much attention has been directed to carcinogens produced by tobacco combustion; the possible effects of nicotine on the tissues in relation to cancer should now be investigated.

If it were shown that metabolic changes are caused by smoking tobacco, and since it is known that nicotine can pass through the placental circulation, the effects of nicotine on the developing foetus should be studied. Is it possible that cellular changes may be caused *in utero* which manifest their effects in later life?

In the prevention of lung cancer people should be dissuaded from beginning to smoke and smokers persuaded to stop. This is a great challenge to all, and doctors should help people to overcome a severe form of drug addiction. I have made some practical suggestions to help towards a solution of this problem (Raven, 1957), for I feel that elimination of the tobacco habit could be one of the greatest benefits conferred by preventive medicine.

Conclusion

The prospects of cancer control are hopeful, but much work still remains to be done before we reach our objective. A greater international effort is required, more effective use should be made of our present knowledge, and new ideas and clues are urgently required.

I wish to thank Mr. P. M. Payne and Mr. M. D. Staunton for kindly analysing the results of adrenalectomy, and I appreciate the kindness of my colleagues at the Royal Marsden Hospital for allowing me to publish them. I am grateful to Dr. H. E. M. Kay for supplying the foetal thyroids.

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Twelve identical travelling exhibitions on Britain's care of the blind are being sent by the British Council to more than 50 countries overseas. The exhibitions will be touring in Europe, the Middle and Far East, Australasia, Africa, South America, and the West Indies during the next two years. The exhibitions, prepared by the Council with the help of blind welfare organizations, each consist of over 100 photographs showing how blind people in Britain are helped and taught to help themselves. With the exhibitions go periodicals in Braille and Moon type and the publications of official and voluntary organizations for the blind. The majority of countries will show films on the care and treatment of the blind in Britain and the Commonwealth. The exhibitions are intended primarily to show welfare workers and social workers what can be done for people with no sight, but there is also material of wide general interest. There are sections devoted to the following aspects of the subject: the responsibility of the Government, local authorities, and voluntary organizations towards the blind; work for blind children and young people; the rehabilitation of the newly blind; training and employment of blind people here and in the Commonwealth, and equipment for the blind—ranging from bread-cutters for blind housewives to "talking books" recorded on tape.

FACTORS INFLUENCING* RESPONSE TO HYPOPHYSECTOMY FOR ADVANCED CANCER OF BREAST

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The value of hypophysectomy in the treatment of patients with advanced cancer of the breast has been well established. There is not, however, general agreement about which patients are most likely to respond, and many who undergo operation do not benefit from it.

Several factors appear to have influenced the result in some series. The most discriminating so far reported is a function, calculated from the levels of 17-hydroxy-corticosteroids and aetiocholanolone in the urine, which shows a close correlation with the clinical result (Bulbrook *et al.*, 1960). The method, however, involves elaborate chemical procedures, which are not generally available, and the conclusions await confirmation.

Analyses of other factors, obtained by clinical methods, by simple diagnostic procedures, or by observation of the effects of simple therapeutic measures, have been reported.

Age.—The age of the patient at the time of operation appears to be unimportant. Thus Pearson and Ray (1960) found that the results tended to improve with increasing age, while others (Baron *et al.*, 1958; Luft *et al.*, 1958; Evans *et al.*, 1959; Atkins *et al.*, 1960) have not observed that age has any effect.

Relation to Menopause.—Several authors have reported that patients who are still menstruating are more likely to respond favourably to operation than those who have passed the menopause or who have undergone oophorectomy; while others (Atkins *et al.*, 1960) have not observed any such influence. The results which have been published in comparable form are shown in Table I. The bulk of the evidence seems to support the contention that the pre-menopausal state has a favourable influence on the outcome of hypophysectomy.

*In this paper the word "influencing" is to be understood as "associated with and preceding in time." It does not necessarily imply a cause-and-effect relationship.

Total Duration of Disease.—Patients in whom the disease has developed slowly seem more likely to respond well than those in whom it has progressed rapidly. Thus the response is better in those with a long interval of time between the first appearance of the carcinoma (Luft *et al.*, 1958; Atkins *et al.*, 1960), or the primary mastectomy (Pearson and Ray, 1960), and the hypophysectomy than in those in whom the interval is short.

Histological Structure of Tumour.—There is no correlation between the histology of the tumour and the response (Baron *et al.*, 1958; Evans *et al.*, 1959).

Sites of Lesions.—Pearson and Ray (1960) noted that patients with metastases in bone (with or without other lesions), lymph nodes, and lung responded more often than those with lesions at other sites. Others (Luft *et al.*, 1958; Baron *et al.*, 1958; Evans *et al.*, 1959) have not observed that the sites of the lesions have any consistent influence on the response.

Response to Previous Endocrine Therapy.—It has been noted repeatedly that patients who have previously responded well to treatment with hormones or to oophorectomy are more likely to obtain benefit from hypophysectomy than those who have failed to do so.

TABLE I.—*Influence of Menopause on Clinical Result of Hypophysectomy*

Authors	Pre-menopausal		Post-menopausal*	
	Total	Improved	Total	Improved
Luft <i>et al.</i> (1958)	15	10 (67%)	30	16 (53%)
Baron <i>et al.</i> (1958)	14	12 (86%)	19	10 (53%)
Evans <i>et al.</i> (1959)	5	4 (80%)	26	7 (27%)
Pearson and Ray (1960)	20	12 (60%)	275	130 (47%)

* Natural or artificial.

TABLE II.—*Influence of Response to Previous Endocrine Therapy on Clinical Result of Hypophysectomy*

Authors (and Type of Therapy)	Previous Endocrine Therapy			
	Good Response		Poor Response	
	Total	Improved by Hypo- physectomy	Total	Improved by Hypo- physectomy
Baron <i>et al.</i> (1958) (miscellaneous)	12	8 (67%)	11	1 (9%)
Pearson and Ray (1960) (oophorectomy or x-ray castration)	23	21 (91%)	29	2 (7%)
Evans <i>et al.</i> (1959) (miscellaneous)	13	2 (15%)	6	0 (0%)

The published results are shown in Table II. Atkins *et al.* (1960) do not confirm this finding, but their results are not reported in a comparable manner.

The results of laboratory investigations, other than those of Bulbrook *et al.* (1960), to which we have already referred, have not proved helpful in the prediction of the response to operation.

In previous preliminary reports we concluded (1) that patients who had blood-borne metastases were more likely to respond to hypophysectomy than those in whom the disease had remained localized (Edelstyn *et al.*, 1958), and (2) that the best results were obtained in patients with bony metastases, in those aged 41 to 50 years, and in those who had their operations performed early (McCalister, 1960).

Our present purpose is to examine the factors, known at the time of operation, which appear to have influenced the outcome of hypophysectomy in a larger series.

Material, Methods, Definition of Terms, and General Results of Operation

The series includes 75 women with advanced breast cancer who were treated consecutively by transfrontal hypophysectomy between March, 1957, and February, 1960, and who survived operation for more than three weeks. In 54 the pituitary fossa was packed with yttrium-90 oxide after the gland had been removed (Edelstyn *et al.*, 1958).

The patients were examined clinically before operation, visible lesions were photographed, and x-ray films were taken of the skull, chest, spine, pelvis, humeri,

TABLE III.—*General Results of Hypophysectomy*

Category	No.	No. Dying Within 3 Months
Objective remission ..	32 (43%)	0
Subjective improvement ..	17 (23%)	6 (35%)
No response ..	26 (35%)	11 (42%)
Total ..	75 (100%)	

and femora. After operation they were seen at intervals and appropriate examinations were repeated. The x-ray films were reviewed independently by one of us (J. O. Y. C.).

Three types of response to hypophysectomy were recognized: (1) Objective remission (the best): Objective evidence of regression of major lesions; no progression; no new lesions; relief of pain and other symptoms. (2) Subjective improvement (intermediate): Relief of pain and other symptoms, but no objective evidence of regression. (3) No response (the worst): Disease apparently unaffected by treatment.

The overall results are shown in Table III. Each patient was assigned to the best category achieved during the whole post-operative period. Subjective improvement by itself, although a striking and definite effect of hypophysectomy, is not associated with a significant increase in the survival time and is therefore of questionable benefit. In the analyses which follow we are concerned mainly with the proportions of patients in different groups who achieved objective remission.

Analysis of Three Principal Factors Influencing Response

Of several factors examined, three, which were applicable to all the patients in the series, appeared to influence the result significantly ($P < 0.05$). These were: (1) the sites of the lesions (Table IV); (2) the relation to the menopause (Table V); and (3) the time at which the operation was performed (Table VI). The highest proportions of objective remissions were observed in patients with osseous metastases, in those who were still menstruating, and in those who had their operations early.

Sites of Lesions

The lesions recorded are those which were observed on clinical or x-ray examination before operation. No account is taken of lesions which became apparent later or which were found at necropsy. The term "osseous metastases" refers to lesions in bones distant from the primary site. Local disease is defined as that in the breast, on the chest wall (primary or recurrent), in the underlying pleura, or in the regional lymphatic glands. Visceral metastases are those in distant viscera, particularly the lungs and the liver. Patients who had osseous

metastases, whether or not they were accompanied by local visceral lesions (the "osseous" group), fared far better than those who had local disease or visceral metastases only (the "soft-tissue only" group) (Table IV). The effect of this factor was most pronounced in

TABLE IV.—*Influence of Sites of Lesions on Clinical Response to Hypophysectomy*

Sites of Lesions	Total	Objective Remission
"Osseous":		
Osseous metastases only	29	15 (52%)
" " + local disease	15	9 (60%)
" " + visceral metastases	8	3 (37%)
"Soft tissue only":		
Local disease only	16	4 (25%)
Visceral metastases only	3	0 (0%)
Local disease + visceral metastases	4	1 (25%)
Total	75	32

If the proportions 27/52 and 5/23 are compared, $\chi^2 = 5.915$, $0.02 > P > 0.01$.

the pre-menopausal patients, but was also apparent in the post-menopausal group and in those who had their operations early or late (Table VII, e, f, j, k). The outcome was not influenced by the presence of the primary lesion at the time of hypophysectomy. Objective remissions were observed in 7 of 15 (47%) in whom the primary was still present, and in 25 of 60 (42%) who had undergone mastectomy previously. The presence of visceral metastases, even in those with osseous lesions, appears to have had an adverse influence on the prognosis.

Relation to Menopause

Remissions occurred in a higher proportion of patients who were still menstruating than of those who had had a natural menopause or who had undergone oophorectomy. The proportions in the two latter groups were similar (Table V). The effect of this factor was apparent

TABLE V.—*Influence of Menopause on Clinical Response to Hypophysectomy*

Relation to Menopause	Total	Objective Remission
Pre-menopausal	21	13 (62%)
Artificial menopause	21	7 (33%)
Natural " "	33	12 (36%)
Total	75	32

If the proportions 13/21 and 19/54 are compared, $\chi^2 = 4.41$, $0.05 > P > 0.02$.

in the osseous group and in those who had their operations early or late (Table VII, a, l, m). In those with soft-tissue lesions, however, remissions were observed only in the post-menopausal group, but this apparent reversal of the effect could easily have arisen by chance, as there were only four pre-menopausal women for comparison (Table VII, b).

Time of Operation

The patients were divided into two groups, according to whether they underwent hypophysectomy "early" or "late." In the former the operation was performed within six months of the disease becoming uncontrolled, as judged by clinical and radiological assessment. In the latter the interval was greater than six months. In the case of those who had been treated effectively (albeit temporarily) by endocrine methods or by radiotherapy the time was measured from the onset of the final recrudescence to the hypophysectomy. The "early" group contained a higher proportion of objective remissions than the "late" group (Table VI), although the difference is not quite significant. However, if patients experiencing subjective improvement are included also,

the difference becomes highly significant. When the effect of the time of hypophysectomy is considered in relation to the other two factors (Table VII, c, d, g, h) it will be seen that an early operation had a slightly beneficial effect which, though not significant, was consistent.

The total duration of the disease from the appearance of the primary breast cancer to hypophysectomy did not have any influence on the result (Table VIII).

TABLE VI.—*Relation of Time of Hypophysectomy to Clinical Response*

Time of Operation*	Total	Objective Remission	Objective Remission plus Subjective Improvement
Early	45	23 (51%)	35 (78%)
Late	30	9 (30%)	14 (47%)
Total	75	32	49

* The terms "early" and "late" are defined in the text.
If the proportions 23/45 and 9/30 are compared, $\chi^2 = 3.28$, $0.1 > P > 0.05$.
" " " 35/45 " 14/30 " " $\chi^2 = 7.69$, $0.01 > P > 0.001$.

TABLE VII.—*Influence of Combinations of Factors (in pairs) on Clinical Response to Hypophysectomy*

Factors	Total	Objective Remission	χ^2 *	Probability
(a) Osseous { Pre-menopausal Post-menopausal	17 35	13 (76%) 14 (40%)	6.06	0.02 > P > 0.01
(b) Soft tissue only { Pre-menopausal Post-menopausal	4 19	0 (0%) 5 (26%)		0.35
Total	75	32		
(c) Osseous { + early operation + late " "	34 18	19 (56%) 8 (44%)	0.43	0.7 > P > 0.5
(d) Soft tissue only { + early operation + late " "	11 12	4 (36%) 1 (8%)		0.13
Total	75	32		
(e) Pre-menopausal { + osseous + soft tissue only	17 4	13 (76%) 0 (0%)		0.01
(f) Post-menopausal { + osseous + soft tissue only	35 19	14 (40%) 5 (26%)	1.06	0.5 > P > 0.3
Total	75	32		
(g) Pre-menopausal { + early operation + late " "	16 5	11 (69%) 2 (40%)		0.26
(h) Post-menopausal { + early operation + late " "	29 25	12 (41%) 7 (28%)	1.06	0.5 > P > 0.3
Total	75	32		
(i) Early operation { + osseous + soft tissue only	34 11	19 (56%) 4 (36%)	1.26	0.3 > P > 0.2
(k) Late operation { + osseous + soft tissue only	18 12	8 (44%) 1 (8%)		0.04
Total	75	32		
(l) Early operation { + pre-menopausal + post-menopausal	16 29	11 (69%) 12 (41%)	3.08	0.1 > P > 0.05
(m) Late operation { + pre-menopausal + post-menopausal	5 25	2 (40%) 7 (28%)		0.86
Total	75	32		

* Where no χ^2 value is shown the probabilities are exact (single tail).

TABLE VIII.—*Relation of Total Duration of Disease (Before Hypophysectomy) to Clinical Response to Operation*

Duration in Years	0-	1-	2-	3-	4-	5-	6-	7+	Total
Objective remission	3 (9)	6 (28)	7 (50)	4 (62)	4 (75)	3 (84)	1 (87)	4 (100)	32
Subjective improvement	3 (18)	3 (35)	3 (53)	2 (65)	1 (71)	1 (76)	1 (82)	3 (100)	17
No response	4 (15)	6 (38)	4 (54)	3 (65)	4 (81)	2 (88)	2 (96)	1 (100)	26
Total	10 (13)	15 (33)	14 (52)	9 (64)	9 (76)	6 (84)	4 (90)	8 (100)	75

The figures in parentheses are cumulative percentages.
If the durations are regrouped as "0-," "2-," and "5+," $\chi^2 = 1.302$; D. of F. = 4; $0.9 > P > 0.8$.

Other Factors

Age.—Age alone did not appear to influence the result as much as the relation to the menopause (Table IX). The highest proportion of objective remissions was seen in patients aged 41 to 50. The fact that a smaller proportion was found in those under 41 is partly explained by the fact that this group contained a larger number who had been treated by oophorectomy and who were therefore post-menopausal.

Influence of Previous Endocrine Therapy.—Forty-eight patients had been treated previously by simpler forms of endocrine therapy (androgens, oestrogens, corticoids, or oophorectomy). Two who had undergone adrenalectomy are excluded from the analysis. The result of therapy is recorded simply as "good" or "poor." A good response appears to have favoured objective remission after subsequent hypophysectomy in patients with lesions of soft tissue only (and here the numbers are small), but not in those with osseous metastases (Table X). A further comparison has been

TABLE IX.—*Influence of Age on Clinical Response to Hypophysectomy*

Age in Years	Total	Objective Remission
—40	16	5 (31%)
41–50	30	17 (57%)
51–60	24	8 (33%)
61+	5	2 (40%)
Total ..	75	32

TABLE X.—*Influence of Previous Endocrine Therapy on Response to Hypophysectomy*

Previous Endocrine Therapy	Result	No.	Objective Remission	χ^2 and P (a v. b)	χ^2 and P (a+b v. c)
<i>All Patients</i>					
Used (a)	Good	14	8 (57%)	0.1 > P > 0.05	2.32 0.2 > P > 0.1
(b)	Poor	34	10 (29%)		
Not used (c)	—	25	14 (56%)		
Total ..		73*	32 (44%)		
<i>Osseous Metastases</i>					
Used (a)	Good	11	5 (45%)	0.088 0.8 > P > 0.7	3.84 P = 0.05
(b)	Poor	20	8 (40%)		
Not used (c)	—	20	14 (70%)		
Total ..		51	27 (54%)		
<i>Soft Tissue Only</i>					
Used (a)	Good	3	3 (100%)	Exact P (single tail) = 0.015	Exact P (single tail) = 0.23
(b)	Poor	14	2 (14%)		
Not used (c)	—	5	0 (0%)		
Total ..		22	5 (23%)		

* Two patients who had had adrenalectomy plus oophorectomy performed prior to hypophysectomy are excluded from this analysis.

made between those who received preliminary endocrine therapy and those who were treated by immediate hypophysectomy. There was no obvious difference initially between the two groups, but the patients were not allocated to them at random. Furthermore, an unknown number of patients who received simple therapy died without being subjected to hypophysectomy. If the data are accepted at their face value it would seem that, in the osseous group, those who underwent immediate hypophysectomy did better than those who had previously received simple endocrine therapy. In those with soft-tissue lesions only, immediate hypophysectomy did not have any such beneficial effect.

Histology of Tumour.—The histological appearance of the carcinoma did not influence the result of hypophysectomy.

Discussion

Three factors which were assessable before operation appear to have had a major influence on the result of hypophysectomy in our series. (1) Those patients who showed x-ray evidence of osseous metastases, either alone or combined with other lesions, responded better than those who had local disease or visceral metastases only. This observation partly confirms the observations of Pearson and Ray (1960), but conflicts with those of most other reports. We have no reason to doubt its validity. (2) The influence of the menopause has been observed by four other groups of workers (Table I), and it seems probable that better results are generally obtained in pre-menopausal patients. The menopause is almost certainly a more important factor than age. The new observation, which requires confirmation because of the relatively small numbers (Table VII, b), is that those with lesions in the soft tissues only, seem more likely to respond to hypophysectomy *after* the menopause than before. (3) The effect of early operation does not appear to have been examined before. It is, however, reasonable to suppose that the longer the disease is left untreated the more likely it is to become independent of hormonal control. The period of six months seems to be fairly critical, since most of our patients were operated on within 12 months of the disease becoming uncontrolled and the period of 6 to 12 months contained most of the failures.

No previous comparison appears to have been made between the results of immediate hypophysectomy and those of simple endocrine treatment followed later by hypophysectomy. Our data suggest that patients with osseous metastases who underwent hypophysectomy as the first endocrine manoeuvre fared better than those who received simple endocrine therapy first. However, although many patients in both groups are still alive, it is likely that the survival period from the time of starting endocrine therapy of any sort (hypophysectomy or simple therapy) will prove to be greater in those who received simple endocrine therapy first. These matters can be resolved only by a controlled therapeutic trial.

Knowledge of the chances of an objective remission after operation is clearly important. The factors with which we are concerned are, as we have stated already, those which are apparent clinically and radiographically at the time of hypophysectomy. The best results were obtained in premenopausal women with osseous metastases (Table VII, a, e), 76% (S.E.10.3%) of whom had remissions. In a larger series we could expect (with 95% confidence) that at least 55% would benefit and that as many as 97% might possibly do so. Operation can certainly be recommended for this group, but we would be very hesitant to advise it in those with soft-tissue lesions only, especially before the menopause. Other combinations of factors are intermediate in their prognostic significance.

These conclusions have been reached retrospectively and empirically, but until we have a better understanding of the nature of hormone dependence of breast cancer they should provide a useful guide to the selection of patients for hypophysectomy.

Summary

The factors which influenced the response to hypophysectomy for advanced cancer of the breast in women were analysed in 75 consecutive patients who survived operation.

The following proportions of patients in different groups underwent objective remission: Whole series, 32/75 (43%). Those with osseous metastases, 27/52 (52%); without osseous metastases, 5/23 (22%). Pre-menopausal patients, 13/21 (62%). Post-menopausal patients, 19/54 (35%). Those who had their operations within six months of the disease becoming uncontrolled, 23/45 (51%); more than six months, 9/30 (30%). Pre-menopausal patients with osseous metastases, 13/17 (76%).

Previous endocrine therapy influenced the response in various ways.

Age, the total duration of the disease, and the histological structure of the tumour did not influence the result.

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OESTROGEN EXCRETION OF PATIENTS WITH BREAST CANCER*

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By means of the more sensitive assay techniques now available it has been established that oestrogens may persist after oophorectomy and adrenalectomy in the urine of patients suffering from breast cancer. Jessiman (1958), using the bio-assay technique of Smith and Smith (1952), reported the presence of oestrogens after oophorectomy and adrenalectomy, while Dao (1953), also measuring biological activity, had found a fall in oestrogen levels after castration but complete disappearance after adrenalectomy. Chemical determinations by the Brown method (Bulbrook and Greenwood, 1957; Greenwood and Bulbrook, 1957; Bulbrook, Greenwood, Hadfield, and Scowen, 1958) indicated the persistence of oestrone (OE), oestradiol (OD), and oestriol (OT) in urine after both these operations and also after hypophysectomy. Although Diczfalussy and his colleagues (1958) questioned the nature of the small quantities of oestrogen-like chromogens

measured by the Kober reaction used in Brown's method, parallel chemical and biological assays by Bulbrook, Greenwood, and Williams (1958) confirmed the presence of oestrogenic activity in urine extracts from post-operative patients where small amounts of these substances had been determined chemically.

Since it was suggested many years ago that the continued growth of mammary carcinoma might be dependent on oestrogenic hormones and improvement could be achieved by removal of the ovaries, many comparisons have been made between the quantities of oestrogens excreted by patients with breast cancer and their clinical condition, but no correlation has yet become apparent.

The aim of this present investigation was to study oestrogen excretion in conjunction with subsequent clinical progress to see if pre-operatively it might be possible to predict from the hormone picture a patient's response to oophorectomy or adrenalectomy. The post-operative progress was compared with any alteration in amounts or pattern of hormone excretion caused by the operation; and in addition the histology of the primary tumour was reviewed in connexion with oestrogen levels and response to treatment.

Methods

The methods used were those of Braunsberg, Osborn, and Stern (1954) and Braunsberg, Stern, and Swyer (1954) for OE and OD, utilizing partition chromatography and fluorimetry; OT was measured by Brown's method, including the additional purification step (Brown, 1955; Brown, Bulbrook, and Greenwood, 1957).

Assays were made on 24-hour urine specimens collected before operation and, in most cases, within three weeks afterwards. It proved very difficult to obtain additional specimens once the patients had left hospital, so only the results of immediate post-operative determinations were available for comparison, and it was not known what further changes might have occurred during the subsequent course of the disease.

Vaginal smears were usually taken on the same day as the urine collection and stained with Shorr's stain. The percentages of cornified and basal cells were recorded.

Fifteen pre-menopausal women, whose ages ranged from 37 to 50, with an average of 45, were investigated before and after oophorectomy. Five others, aged between 37 and 51, who had previously been castrated, underwent adrenalectomy. A further four patients aged 38 to 66 had a combined operation in two stages—namely, bilateral oophorectomy and unilateral adrenalectomy, followed 14 days later by removal of the second adrenal.

Assessment of the effect of hormone ablation was often very difficult and depended on clinical impression rather than definite evidence. Patients showing signs of regression of bone metastases, even temporarily, disappearance of skin metastases, or alleviation of bone pain were classed as "improved." Also described as improved were cases where there was some indication that life had been prolonged in a state reasonably free from distress. In a number of patients the clinical response was either equivocal, in which case they were grouped with the "not improved," or it was too early after the operation for assessment to be made.

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