works in equal partnership with her medical and non-medical colleagues. . . . She contributes to a more comprehensive diagnosis by adding her knowledge about the psycho-social aspects of the patient's functioning, their relationships and the social system in which they move."⁸

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For Debate

Hypothesis: Breast Cancer Regression under Oestrogen Therapy

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Summary

Recent reports have thrown doubt on both of the major mechanisms which have been suggested for the regression of breast cancer under high-dosage oestrogen therapy—a direct effect on binding sites and an indirect inhibition of prolactin release. A searching review on the clinical response of 407 patients with advanced breast cancer treated by oestrogen therapy under my direction showed certain anomalies, including age determined tumour inhibition and stimulation, dose dependence of tumour inhibition and stimulation, differential site sensitivity, and tumour regression with oestrogen withdrawal. The hypothesis usually postulated to explain these anomalies is that the tumour may in the same individual be composed of multiple genetically distinct clones of cells. It is suggested instead that the effect of high-dosage oestrogen therapy in breast cancer may depend critically on the absolute and relative concentrations of prolactin and oestrogen actively available at the tumour. On this basis the clinical manifestation of tumour stimulation in response to oestrogen administration suggests that the oestrogen concentration at the target is inadequate. Differences in site sensitivity in the same patient may depend on tumoral factors such as the level of oestradiol and prolactin binding receptors in the tissue.

Introduction

For many years it has been assumed by analogy with experimental mammary cancer that oestrogen is necessary to maintain the growth of hormone-sensitive mammary cancer in man. In recent years the presence of high-affinity oestradiol receptor

protein has been shown both in the cytoplasm and in the nucleus of about half of all human mammary cancers examined, and this has led to the suggestion that the presence of oestrogen receptor protein is a major factor in determining hormonal dependence in breast cancer.¹

It should follow that those tumours showing high specific oestrogen binding activity in vitro (or alternatively high uptake of labelled oestradiol in vivo) would be the ones likely to show regression after ablation of the ovaries or adrenal or pituitary glands. Such a relationship has indeed been claimed in two series of patients^{1 2} but was not confirmed in a more recent one.³ It should also be mentioned that in the latter series oestrogen receptor protein was much more frequently found in the breast cancer of the older patients than in the younger ones,⁴ and the significance of this observation is discussed below.

In the postmenopausal woman breast cancer may regress with high-dosage oestrogen therapy as well as after endocrine ablation. The mechanism for this apparently paradoxical response is not clear. Though it is commonly assumed that the direct effect of oestrogen on the cells of all target organs must be mediated by the specific receptor binding sites, in the case of breast cancer it has recently been reported that the likelihood of regression under high-dosage oestrogen therapy cannot be correlated either with a high or with a low level of oestradiol uptake in the tumour tissue.³

It is, of course, possible that high-dosage oestrogen administration can affect the growth of tumour cells by a local cell mechanism other than through the binding sites. It has been suggested that such mechanisms might include an effect on the permeability of the cell membrane or of the subcellular membranes.⁵ The oestrogen therapy of breast cancer involves a dose which is at least 10 times that used generally in the treatment of gynaecological disorders, and it has been shown that the effect of oestradiol on DNA synthesis in mammary tissue in vitro is dose dependent.⁶ According to its concentration it may either stimulate or inhibit DNA synthesis.

It is likely also that administration of oestrogen can exert indirect effects on breast cancer growth either by stimulating the immune mechanism^{7 8} or by an effect on anterior pituitary secretion.^{9 10} Thus for some years it has been suggested that the major effect of high-dosage oestrogen therapy in hormone-sensitive mammary carcinoma is to deprive the tumour of the mitosis-stimulating effect of prolactin, and the mechanism was

assumed to be by inhibition of prolactin release from the anterior pituitary gland.¹¹ This assumption, however, is no longer tenable owing to the recent finding both in rats¹² and in man¹³ that a high dosage of oestrogen stimulates the release of prolactin.

Hypothesis

It appears, therefore, that recent reports have thrown doubt on both of the major mechanisms which have been suggested in the past for the regression of breast cancer under high-dosage oestrogen therapy—a direct effect on binding sites and an indirect inhibition of prolactin release. Though its basis is empirical oestrogen therapy is the simplest and most efficacious method of endocrine therapy in the older patient. Improvement in its results can come only from an understanding of its mechanism. It was therefore decided to searchingly review the characteristics of clinical response and the factors associated with tumour regression in 407 patients with inoperable or recurrent breast cancer treated by oestrogen under my direction. It was thought that certain anomalies and paradoxes which have been observed in the clinical response might provide a clue to the mechanism involved.

It is postulated from this review that the nature of the tumour response, whether inhibition or stimulation of growth, may depend on the absolute and relative concentrations of prolactin and oestrogen which are actively available at each tumour site. This working hypothesis is also compatible with recent observations on the effect of high doses of oestrogen on hormone-responsive mammary carcinoma in rats.¹⁴ It is nevertheless likely that there are other factors in addition to the hormonal environment which help to determine the degree and duration of response in breast cancer to high-dosage oestrogen therapy. Our knowledge is still undeveloped, but these factors influencing clinical response to oestrogen therapy in the individual patient can be divided into tumoral factors, host factors, and hormonal factors.

Tumoral Factors.—Response may depend on (1) the heterogeneity of the cell population in the individual mammary cancer and the genetically determined hormonal sensitivity of each clone (this may be related to receptor site levels in each clone); (2) the degree of cell differentiation existing in the tumour, the more differentiated the tumour the more important the carcinostatic or maturation mechanism¹⁵; (3) the stage of tumour growth, as the later phases of malignant growth appear to show an increased tendency to autonomy in experimental animals.

Host Factors.—Response may depend on (1) the hypothalamic feedback mechanism, as exemplified by a different response in the premenopausal woman from that in the postmenopausal woman; (2) the site of metastasis as biochemical and vascular factors in the stroma appear to influence the degree of response from site to site; (3) the stage of the disease as later stages appear to be associated with failure of the immunosurveillance mechanism in the host.

Hormonal Factors.—Response may depend on (1) the type of oestrogen, its route of administration, and its metabolism; (2) the absolute and relative concentrations of oestrogen and prolactin actively available at each site of the tumour.

It is the hormonal factors which are especially considered in this study.

Tumour Inhibition and Stimulation

The criteria of regression and other statistical aspects of the 407 patients have been reported elsewhere¹⁶ and are not repeated here. The only other large series of oestrogen-treated cases reported in the literature is one of 364 cases collected from multiple sources,¹⁷ and such a series cannot provide the information which is possible from a searching review of a personally

observed series. All patients were followed up for at least five years or until death. Treatment was either stilboestrol 1.5 to 15 mg daily or ethinyloestradiol 1.5 to 3 mg daily or Premarin 7.5 to 15 mg daily. These agents and doses have been shown to yield similar regression rates in the treatment of breast cancer.^{18 19} Oestrogen was the primary method of endocrine therapy in 347 of the patients, but in 60 it was secondary to another method of endocrine therapy, mainly androgen administration, though in a few cases corticosteroid therapy or castration was used.

TABLE I—Regression of Breast Cancer from Oestrogen Therapy in relation to Number of Years Past Menopause

Years Postmenopausal	No. with Tumour Regression		Significance
	A	B	
0 to 5	4 of 59	3 of 23 (13%)	} P < 0.05
6 to 9	7 of 30	7 of 24 (29%)	
10 and over	79 of 299	75 of 197 (38%)	
Overall regression rate ..	23%	35%	

A, Excludes cases given concomitant radiotherapy.

B, Excludes also cases treated for 1 month or less and those treated secondarily by oestrogen.

The crude regression rate from high-dosage oestrogen therapy in my series is 23%, but the net regression rate is 35% if patients receiving oestrogen for less than one month and those treated secondarily by oestrogen are excluded (table I). The selected group obviously provides a more exact assessment of the value of oestrogen therapy because, on the one hand, it is impossible to establish tumour regression in less than six weeks of treatment and, on the other, it is generally agreed that the results of secondary hormone therapy are much inferior to those of primary therapy. The selected group is used for comparison of response within the series because of its greater significance.

Age Dependence and Hormonal Environment

It has long been noted that the likelihood of tumour regression from high-dosage oestrogen therapy tends to increase with age.¹⁸ Table I shows the progressive rise in regression rate with each five-year period after the menopause. Because the exact age at the menopause is rarely remembered with any degree of certainty in the older woman it was thought to be more accurate in patients over 60 to analyse the regression rate according to chronological age. Rates are found to rise progressively with each decade without any suggestion of a peak or plateau (table II). In patients over 80 treatment by oestrogen yields the remarkably high regression rate of 59% in the selected group, and there is no evidence to support the suggestion that the regression rate from oestrogen therapy peaks at eight years after the menopause.¹⁹

TABLE II—Regression of Breast Cancer from Oestrogen Therapy in relation to Age

Age	No. with Tumour Regression		Significance
	A	B	
Up to 59	11 of 87	11 of 62 (18%)	} P < 0.01
60 to 69	30 of 131	29 of 90 (32%)	
70 to 79	20 of 91	18 of 46 (39%)	
80 and over	29 of 79	27 of 46 (59%)	

A, Excludes cases given concomitant radiotherapy.

B, Excludes also cases treated for 1 month or less and those treated secondarily by oestrogen.

Clarification of this age-related response to oestrogen is important because of its possible relationship either to a genetically determined characteristic of the tumour or to its hormonal environment, and this is discussed below. A possible reason why

the remarkably high regression rate in older patients has not been made clear in other series is that with increasing age there is a greater tendency to discontinue oestrogen prematurely. This lowers the crude response rate. Thus in patients over the age of 70 oestrogen was discontinued in 78 out of 170 patients before the completion of one month of treatment (table III). In only 18 of the cases was this due to serious side effects such as severe vomiting or cardiac embarrassment. With encouragement the younger patient will usually accept mild loss of appetite, oedema of the ankles, or stress incontinence of urine, but in the elderly patient these usually lead to insistence on a change in therapy, with consequent loss of the very high likelihood of tumour regression possible in this age group.²⁰

An attempt was made to correlate the age-related rise in tumour regression from oestrogen therapy with the hormonal environment as reflected in the cytohistological pattern of the vaginal smear. The two main patterns observed in the postmenopausal vaginal smear have been classed as teleatrophy and oestatrophy. Teleatrophy is associated with an atrophic vaginal mucosa and indicates a complete absence of stimulation by oestrogen and androgen. A pattern of oestatrophy, on the other hand, typically shows predominance of intermediate cells, but it is not certain whether this reflects postmenopausal secretion of oestrogen or of androgen or of both.

TABLE III—Response to Oestrogen Therapy by Breast Cancer in Patients aged over 70. Figures exclude Cases given Concomitant Radiotherapy

	No. of Cases
Reason why oestrogen therapy was discontinued:	
Toxicity	18 (Excluded)
Inadequate trial	60 (Excluded)
Response when oestrogen was continued:	
Regression of tumour	45 (49%)
No regression of tumour	47 (51%)
Total	170

When the pretreatment vaginal smear pattern was analysed by age group in 200 postmenopausal patients with breast cancer (table IV) it was noted that the proportion with teleatrophy tends to increase progressively with increasing number of years past the menopause. This tendency, however, is not related to the age-related rise in tumour regression rate from oestrogen therapy.²¹ In the 102 patients whose vaginal smear was examined before oestrogen therapy there was no significant difference in regression rate between those with teleatrophy (37%; 21 out of 57) and those with oestatrophy (31%; 14 out of 45). This suggests that the age-related rise in the regression rate from oestrogen therapy is associated with some factor other than changes in steroid secretion. This may possibly be an age-related rise in the hypothalamic threshold to oestrogen,²² and this is discussed below.

TABLE IV—Relation of Pretreatment Vaginal Smear Pattern to Age

Years Postmenopausal	Proportion with Teleatrophy	Significance
0 to 5	27 of 70 (39%)	} P < 0.05
6 to 20	38 of 82 (46%)	
21 and over	28 of 48 (58%)	

Age Dependence and Dosage

Though increase in bone pain at the site of a metastasis may represent stimulation of the immunosurveillance mechanism, and the cause of hypercalcaemia in breast cancer is uncertain, their appearance after the onset of oestrogen therapy is usually

taken to represent evidence of tumour stimulation.^{23 24} Exacerbation of pain at the site of established or suspected metastases in bone was noted in only eight patients in the series, but its likelihood was five times greater in patients within nine years of the menopause than in those 10 or more years postmenopausal. Hypercalcaemia was recorded in only three of the 58 patients with bone metastases treated by oestrogen, but again all three were within nine years of the menopause.

The effect of a given dose of oestrogen on breast cancer, whether it is to be inhibitory or stimulatory, is well known to be age dependent. While in the premenopausal patient 15 mg stilboestrol daily usually stimulates tumour growth,^{25 26} tumour regression can be achieved in a proportion of premenopausal patients by the relatively massive dose of 1 g stilboestrol daily.^{27 28} While stimulation of tumour growth may sometimes occur from 1.5 to 15 mg stilboestrol daily in the early postmenopausal patient, risk of stimulation decreases and the likelihood of tumour inhibition from this dose increases with the number of years past the menopause. *Thus the level of oestrogen dosage at which tumour stimulation is replaced by inhibition tends to decrease with increasing age of the patient.*

Oestrogen Utilization in Tissues

There is a level of oestrogen dosage below which there is no effect on the growth of mammary cancer, in the form of either inhibition or stimulation, and this level is probably below 1 mg stilboestrol daily. A recent report has shown that stilboestrol 0.6 mg daily is insufficient to cause regression of breast cancer,²⁹ while the author has shown in a randomized series that 1.5 mg stilboestrol daily yields a similar regression rate in breast cancer (54%; 15 out of 28 cases) to 15 mg daily (55%; 30 out of 55 cases) in patients treated for more than one month. There is, however, evidence that doses of stilboestrol higher than 15 mg daily may achieve tumour control when this dose loses its effect.¹⁶

When the cytohistological pattern of the vaginal smear is reviewed serially in patients receiving oestrogen therapy²¹ it is found that the appearance of a more-prolonged and higher degree of keratinization is more likely to be associated with regression of breast cancer (table V). This may suggest either a greater tumour response with better utilization of oestrogen in the body or that the sensitivity of the normal target tissue in the body to oestrogen runs parallel to the sensitivity of the tumour.

TABLE V—Effect of Oestrogen on Vaginal Smear Pattern in relation to Regression of Breast Cancer

Cornification in Vaginal Smear	No. with Tumour Regression	Significance
Marked	13 of 18 (72%)	} P < 0.01
Temporary	16 of 42 (38%)	
Slight	4 of 18 (22%)	

It must be taken into account, however, that the latter varies from site to site. Thus the regression rate was 40% for local soft-tissue tumour, including primary growth, permeation nodules, and metastatic regional nodes (table VI). It was 33% for vis-

TABLE VI—Regression of Breast Cancer from Oestrogen Therapy in relation to Dominant Site of Metastases

Site of Metastases	No. with Tumour Regression		Significance
	A	B	
Local	75 of 262	72 of 181 (40%)	} P < 0.01
Visceral	12 of 68	11 of 33 (33%)	
Bone	3 of 58	2 of 30 (7%)	

A, Excludes cases given concomitant radiotherapy.

B, Excludes also cases treated for 1 month or less and those treated secondarily by oestrogen.

ceral metastases, most of them in lung and pleura, and the high response rate of pulmonary and pleural metastases to oestrogen therapy is well established.³⁰ On the other hand, the regression rate for bone metastases was only 7%, and it was common to see soft-tissue tumour regressing while bone metastases were uncontrolled. The relation between stromal factors and tumoral factors in the response to oestrogen therapy is discussed below.

Biphasic Response and Withdrawal Response

There was a total of 24 patients to whom oestrogen therapy was given in two separate courses with an interval of at least three months between courses. In 19 of these cases there had been tumour regression from the first course of oestrogen therapy. Of these, five showed a second response to oestrogen therapy, and there were four patients who showed a withdrawal response—that is, tumour regression when oestrogen therapy was stopped. There were five patients who did not respond to the first course of oestrogen therapy but who were given a second course. None of these showed tumour regression from the second course of therapy, but one showed withdrawal response when oestrogen therapy was stopped. Two especially interesting cases are presented in detail.

Case 1.—A woman of 81 presented with an inoperable breast cancer fixed to the pectoral muscles and associated with overlying permeation nodules in the skin of the breast. Because of her age primary treatment with ethinyloestradiol 0.5 mg three times a day was prescribed. This was maintained for a period of 11 months and resulted in almost complete disappearance of the breast tumour and skin nodules for a total period of 24 months. When the tumour reactivated hormone therapy was reinstituted and eight months of therapy led to a further tumour regression for 18 months. When the tumour reactivated a second time oestrogen therapy was given for 22 months—this time, for as long as the tumour responded. When finally the tumour reactivated for the third time discontinuing the hormone led to a withdrawal response for eight months. In spite of a fourth attempt at oestrogen therapy the patient died 14 months later.

Case 2.—A woman of 63 presented with breast cancer showing early fixation to the pectoral muscles. She received a course of preoperative x-ray therapy to a mean tumour dose of 4,000 rads in 27 days and this was followed by a radical mastectomy. She presented 12 months later with recurrent nodules in the skin and also radiographically sclerotic bone metastases. Treatment with stilboestrol 5 mg three times a day was prescribed. The skin nodules regressed and she remained free of pain for a period of 18 months, though the bone metastases did not recalcify. Oestrogen therapy was maintained for a further five months, and when it was stopped this led to withdrawal regression of the nodules for a period of 10 months. When the nodules again began to grow stilboestrol therapy was reintroduced and a third regression of tumour was achieved, though for a period of six months only. The patient died five months later.

The first case is of particular interest because of oestrogen-induced regression of soft-tissue tumour on three separate occasions, followed on the last occasion by a withdrawal response. The second case is of interest because of oestrogen-induced regression of tumour on two occasions with a withdrawal response in between. A case reported recently³¹ showed regression of tumour from oestrogen therapy on two occasions, each time followed by a withdrawal response. It is generally assumed that disappearance of tumour control from oestrogen therapy is due to selective death of oestrogen-responsive cells. This does not appear to be a likely explanation in cases such as those described above.

Discussion

Certain anomalies have been mentioned here in the clinical response of breast cancer to oestrogen therapy. They include age dependence of tumour inhibition and stimulation, dose dependence of tumour inhibition and stimulation, differential site sensitivity, and tumour regression with oestrogen withdrawal.

The hypothesis usually put forward to explain these observations is that mammary cancer may, in the same individual, be composed of multiple, genetically distinct clones of cells.³² Some are thought to be inhibited by oestrogen (oestrogen responsive), some stimulated by oestrogen (oestrogen dependent), and some unaffected by oestrogen. Different tumour sites are thought to contain different proportions of each type of cell, thus accounting for differential site sensitivity. Furthermore, when the oestrogen-responsive cells of a tumour die after oestrogen therapy it is assumed that they are replaced either by autonomous cells or by oestrogen-dependent cells. These changes are thought to account respectively for the development of tumour reactivation after continued oestrogen therapy and for the observed cases of withdrawal response.

I have mentioned, however, a decreased tendency to tumour regression and an increased tendency to tumour stimulation by oestrogen in the younger patient—that is, an increased likelihood of oestrogen dependence. If oestrogen dependence runs parallel with the presence of oestrogen binding protein,¹ one would expect binding activity to be more common in the younger patient but, in fact, the opposite may be the case.⁴

The multiple clone hypothesis has been used also to explain observations such as response to high-dosage oestrogen therapy followed by response to oophorectomy in the premenopausal patient²⁸ or response to oestrogen therapy followed by response to hypophysectomy in the older patient.¹⁶ It is, however, unable to explain satisfactorily alternating response to oestrogen administration and to its withdrawal on two or three successive occasions, as described above. On the other hand, it is possible to explain all these anomalous observations on the basis of the hypothesis proposed at the beginning of this paper—that the effect of high-dosage oestrogen treatment in breast cancer may depend critically on the absolute and relative concentrations of prolactin and oestrogen actively available at the target site.

It has been noted in the case of the dimethylbenzanthracene-induced rat mammary carcinoma that the tumour regresses in a proportion of animals after either oophorectomy or adrenalectomy or hypophysectomy or oestrogen therapy—just as it does in the case of the human tumour. The response to oestrogen in the rat tumour varies with the dosage; smaller doses cause stimulation, while larger doses cause inhibition of growth activity.^{33 34} This is not due to a differential effect on prolactin release from the pituitary gland, because both low and high dosage of oestrogen stimulate prolactin release in this animal.¹² The observation of dose dependence in the rat tumour may, however, be explained on the basis that the tumour activity depends on the relative and absolute concentrations of prolactin and oestrogen available at the target site. It has been suggested that oestrogen at high concentration is able to oppose the mitosis-stimulating effect of prolactin by a peripheral mechanism and thus causes inhibition of tumour growth activity.¹⁴

In man, too, it has recently been shown that while high dosage of oestrogen stimulates the release of prolactin from the pituitary gland in postmenopausal women,¹³ the effect of such therapy is often to inhibit the growth of breast cancer. The mechanism may be similar to that which has been suggested above in the case of experimental mammary carcinoma, and in that case will depend on an adequate level of oestrogen administration. This hypothesis emphasizes the value of the vaginal smear pattern as mentioned above for determining the degree of utilization of oestrogen in the patient. It might also provide the reason for the association of a well keratinized vaginal smear pattern with a greater tendency to tumour regression.

There is an important corollary to this hypothesis. If this is the mechanism responsible for the regression of human mammary cancer after oestrogen therapy, then the clinical manifestation of tumour stimulation not only provides evidence of hormonal sensitivity but also suggests inadequate oestrogen concentration at the tumour. Because we are uncertain of the oestrogen mechanism involved it has been the usual practice in such cases to stop oestrogen administration immediately on the appearance of tumour stimulation and to take refuge in

cytotoxic agents or corticosteroid therapy. Yet in patients with hypercalcaemia occurring at the beginning of oestrogen therapy of bone metastases it has been shown that persistence of oestrogen therapy eventually results in objective evidence of tumour regression in the majority.²³ It is therefore rational not only to persist with oestrogen therapy when evidence of tumour stimulation becomes apparent at any site but also to increase oestrogen dosage in order to achieve high concentration at the tumour as quickly as possible. Corticosteroids or symptomatic therapy can still be given concomitantly to relieve the subjective complaints of tumour aggravation.

As observed above, with increasing age of the patient a lower dose of oestrogen is required to inhibit tumour activity in breast cancer, and this may possibly reflect a lower prolactin level to be overcome at the target. Because of decreasing hypothalamic sensitivity with increasing age,²² the same dose of oestrogen might stimulate the release of a relatively lower level of prolactin from the anterior pituitary gland. On the other hand, differences in site sensitivity to oestrogen therapy may be due to tumoral factors. Thus differences in the degree of tumour regression between metastases in different organs, such as liver and lung, are usually ascribed to biochemical differences between the stromal tissues. Differences in the degree of tumour regression from area to area of the same tissue are often ascribed to differences in vascularity. However, regression in one group of lesions under oestrogen therapy while similar lesions elsewhere are showing evidence of active growth may represent differences in the absolute and relative concentrations of prolactin and oestrogen achieved at each target site. This may possibly be associated with variations in hormone binding activity.³

Laboratory studies may help in elucidating the cause of these site differences in response. Thus a biopsy specimen of the tumour may be examined for its level of specific binding receptor for oestradiol¹ (and possibly also for prolactin when the assay is firmly established). The ability of the tumour itself to synthesize or conjugate oestradiol may also be vitally important in relation to its hormonal response.^{35 36} Another approach to the problem is to assess the effect of oestradiol or prolactin in enhancing or depressing pentose shunt activity in an organ culture of the tumour.³⁷ The response may possibly reflect the level of oestradiol and prolactin binding receptors in the specimen examined.

The conclusion to be derived from recent work is that there is unlikely to be a single hormonal relationship or unitary hypothesis capable of explaining the response by human mammary cancer to all methods of endocrine therapy, including high-dosage oestrogen therapy.¹⁵ On the assumption that both prolactin and oestrogen are required for maintaining the growth of hormone-sensitive breast cancer there are two ways by which the same tumour can be made to regress—one by depriving it of both prolactin and oestrogen as far as possible by endocrine

ablation, and the other by increasing the level of the two hormones at the target as a result of high-dosage oestrogen therapy. This hypothesis can explain response to oestrogen therapy followed by response to oophorectomy,²⁸ response to oestrogen therapy followed by response to hypophysectomy,¹⁶ and response to hypophysectomy followed by response to oestrogen-progesterone combination therapy.³⁸ There is no need to postulate the existence of genetically distinct oestrogen-dependent clones and oestrogen-responsive clones in such cases.

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