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Letter to the Editor

Spontaneous Regrowth of Regressed Hormone-dependent Tumours after Long Periods of Time*

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HORMONE-DEPENDENT (HD) mammary tumours have been described in both rats [1–3] and mice [4–8]. Growth of these HD tumours can be arrested by endocrine manipulation that usually results in tumour regression. Sometimes the regression is 'complete', i.e. the tumour becomes undetectable by palpation and is considered to have been eliminated [9, 10].

In the present communication we have caused regression of HD mouse mammary tumour transplants by hormonal deprivation and have studied the regrowth of these tumours.

Mammary adenocarcinomas were induced in ovariectomized mice of the inbred GRS/AFib strain by treatment with progesterone (p) and oestrone (o) [11]. Thirty-three tumours in mammary gland No. 4 or 5 were each transplanted subcutaneously into 2 castrated male mice treated with p + o. When the tumours had reached a size of approximately 1 cm^3 hormone treatment was discontinued in one of the animals, and this animal was observed for one year or until a regrowing tumour had attained a size of approximately 1 cm^3. In order to test the hormone dependence, the other tumour was transplanted to 4 castrated mice, 2 of which received treatment with p + o. If the tumour grew in the hormone-treated and not in the untreated animals it was considered to be hormone-dependent (HD). If it grew equally well in treated and untreated animals it was defined as being hormone-independent (HI), and if it grew more rapidly in the treated animals it was considered to be hormone-responsive (HR).

Nine of the 33 tumours were classified by transplantation criteria as HI or HR and did not regress after hormone deprivation. Fifteen of the 24 HD tumours regressed 'completely', i.e. they became unpalpable within 1–3 months after discontinuation of hormone treatment (Fig. 1). Three of the animals with unpalpable tumour died after 3, 6 and 9 months without palpable tumours (not shown in the figure). All the remaining 12 tumours that had regressed 'completely' reappeared at the site of inoculation and attained a size of approximately 1 cm^3 within 3–12 months after hormone withdrawal. Four of the early regrowing tumours were transplanted in order to test their hormone dependence, and they were all found to be HI.

HD tumours require hormone(s) for their growth. Since tumour growth is the net result of tumour cell production and tumour cell loss a decrease in cell production may not only result in an arrest of growth, but also in tumour regression. The absence of the growth-stimulating effect of hormones has been shown to be an important mechanism in the regression of mammary tumours in GR mice [12]. However, this is probably not the sole mechanism involved in tumour regression. An increased release of lysosomal enzymes has been demonstrated in regressing HD rat mammary tumours [13].

Huggins [9] has previously described how extinction of HD rat mammary tumours could be obtained by endocrine manipulation. However, since the observation periods in his work did not exceed 6 months, or 10 months in a later work [10], possible late regrowth of dormant tumour cells cannot be excluded. Dormant tumour cells were demonstrated in a rat bearing a methylcholanthrene-induced mammary tumour that regressed 'completely' after hypophysectomy. One month after the 'complete' regression, grafting of a mammatropic hormone-producing tumour resulted in the regrowth of the tumour [14]. Oestrogen-dependent rat mammary tumour cells have been shown to remain dormant for 8 months in oestrogen-deficient hosts [15]. Surviving cells

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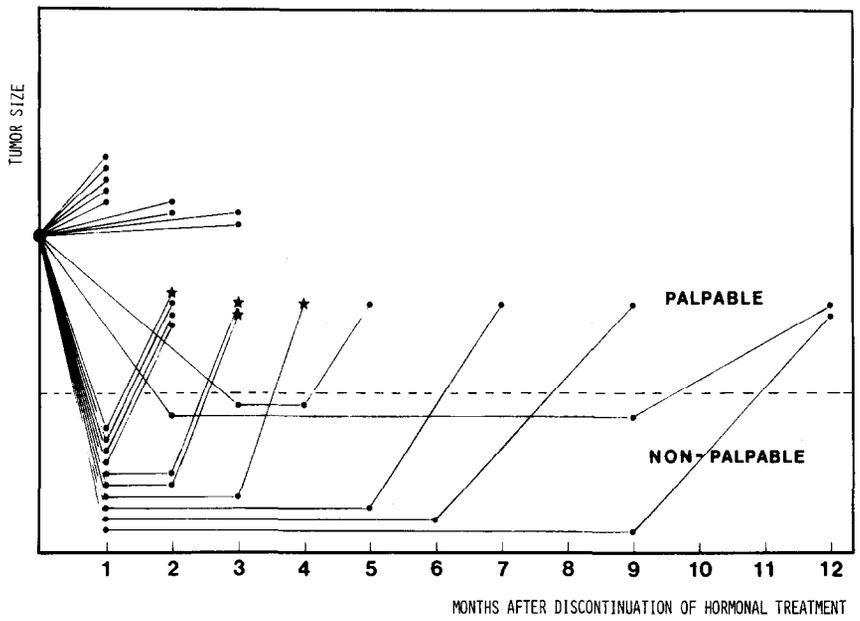

Fig.1. The fate of hormone-dependent GR mouse mammary tumours after discontinuation of hormone treatment. At zero time the tumour size was approx. 1 cm^3 *and the hormone treatment was discontinued. Each full line represents one tumour. A line passing below the dotted line indicates that the tumour size has passed below the detection limit by palpation. An asterix indicates that the regrowing tumour has been transplanted to test the state of hormone dependence.*

were demonstrated by re-administration of oestrone giving rise to tumour. Control animals did not show spontaneous tumour growth; however, the observation period of these animals was not stated.

Although almost half of the HD tumours in the GR mice of the present study regressed 'completely' after discontinuation of hormone treatment, spontaneous tumour regrowth occurred in all animals. Two likely explanations for this regrowth should be considered: (a) the tumour is heterogeneous with respect to cell populations [16]. Hormone deprivation eliminates only HD cells, and the remaining HI cells eventually form a tumour; and (b) all tumour cells are HD and are, therefore, growth-inhibited but not killed. The residual tumour later resumes growth because the cells have progressed to hormone independence.

Early regrowth would be expected if the tumour is heterogeneous and contains HI cells. Late regrowth of pre-existing HI cells can only be explained insofar as the growth rate is lower than that in established HI tumours, in which the doubling time is about 3 days [17]. A single HI tumour cell would result in a palpable tumour (10^8 cells) within less than 3 months provided it proliferates at this rate. Suggestion (b), a progression from the HD to the HI state in the residual tumour cells, offers an alternative explanation for the late regrowth of the tumours. Progression without growth was proposed by Foulds [18] and supported by Noble [19], who demonstrated that suppression of growth may accelerate progression.

Production of oestrogen and progesterone from extragonadal sources may occur in castrated animals, but this is not a likely explanation for regrowth of the tumours since castrated male mice served as hosts for the tumours. It has previously been demonstrated that while spayed female mice supported the growth of an oestrogen-dependent hypophyseal isograft, indicating oestrogen production, male mice did not [20].

The present communication indicates that 'cure' of mammary cancer in experimental animals may not be possible by endocrine manipulations alone either because it results in a selection of HI tumour cells or because residual dormant tumour cells eventually progress to hormone independence.

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