Natural history of breast cancer

Sir,—Dr Schmidt (March 28, p 810) makes several points about our Feb 15 article. His major objections are: (1) that good survival of small tumours may be due to overdiagnosis by screening of non-aggressive tumours ("length bias" cases) or to observed survival being artificially prolonged by lead time; (2) that some small tumours may have a good prognosis despite being systemic; and (3) that tumours whose behaviour is restricted to local spread may be as life-threatening as those that metastasise to distant sites ("Why should breast cancer, acting as a systemic disease, necessarily have a poorer prognosis than disease that progresses locally?). Our responses are:

(1) Our paper was primarily concerned with treatment of the sort of tumours now being diagnosed. It was not intended to be a justification of screening in terms of the results of the two-county trial. Such results have long been known and show a 30% reduction in breast cancer mortality in association with invitation to screening, and these mortality findings are not subject to lead time or length bias. The 30% reduction is consistent with the HIP study, has remained steady over time, and is borne out by the more recent trial in Stockholm. The benefit of a 30% reduction in breast cancer mortality is not questionable, contrary to Schmidt's assertion. To return to the subject of our paper, the treatment of breast cancer, the fact remains that in small tumours, local therapy was sufficient to achieve an excellent prognosis, both in screening detected and in clinically detected tumours. The fact that this result was not due to length bias was evident from the observation that it held good even for grade-3 tumours. It is further borne out by the accompanying figure showing survival by detection mode for tumours less than 10 mm in diameter. The screened and control survival profiles are similarly excellent. Exclusion of the prevalence screen tumours to eliminate most of the length bias and subtraction of three or four years' lead time from the survival of screening detected tumours make no appreciable difference. The conclusion remains that systemic therapy has little or nothing to offer in such cases.

(2) Although theoretically these small tumours may have released malignant cells, our argument, backed up by the data, is that this does not justify systemic therapy. The good prognosis of tumours less than 10 mm in diameter, irrespective of grade or detection mode, shows that our survival results are not invalidated by length bias.

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Oestrogen and progesterone receptor dissociation and family history of breast cancer

Sir,—Several variants of the oestrogen (ER) and progesterone (PR) receptor have been identified but for only a few of them is the functional significance known. Furthermore, alterations in chromosome sequences in the regions of the ER and PR may have an important role in the development of breast cancer. We report that the ER and PR dissociation constants (ERKd and PKd) are significantly reduced in the breast cancers of women with a family history of the disease. This suggests that abnormalities within the receptors themselves are associated with the development of breast cancer.

The women had been referred for radiotherapy and most of them had early tumours. A nurse administered a questionnaire on family
premenopausal women. However, there was no significant difference in the proportion of women with or without a family history who were premenopausal, so menopausal status is not a confounding variable in our study.

An additional factor affecting $K_d$ could be receptor protein status. Multiple polymorphisms of ER and PR have been identified, and the results presented here suggest that some women with a family history of breast cancer might inherit a variant receptor gene with an altered $K_d$. The same inherited structural abnormality might also induce familial breast cancer susceptibility.

**Gene therapy for cancer**

Sir,—Dr Gutierrez and colleagues' review (March 21, p 715) was a useful introduction to some of the gene therapy ideas circulating in cancer research. However, in the context of tumour-cell-targeted gene therapy, insufficient emphasis was given to the important point that the genes must either reach all the target cells or destroy indirectly those tumour cells they cannot reach. Tumour-suppressor genes, MHC genes, and the vari-cella-zoster virus thymidine kinase gene proposed for virus-directed enzyme prodrug therapy (VDEPT) have no "bystander effect" and influence only the tumour cells to which they have been successfully delivered. To cure cancer these genes would have to be delivered to all the patient’s cancer cells but the heterogeneity and inaccessibility of the target cells makes this an elusive goal. 100% efficient delivery of the target cells make this an elusive goal. 100% efficient delivery of the target cells make this an elusive goal. To cure cancer these genes would have to be delivered to all the patient’s cancer cells but the heterogeneity and inaccessibility of the target cells make this an elusive goal. To cure cancer these genes would have to be delivered to all the patient’s cancer cells but the heterogeneity and inaccessibility of the target cells make this an elusive goal. To cure cancer these genes would have to be delivered to all the patient’s cancer cells but the heterogeneity and inaccessibility of the target cells make this an elusive goal. To cure cancer these genes would have to be delivered to all the patient’s cancer cells but the heterogeneity and inaccessibility of the target cells make this an elusive goal. To cure cancer these genes would have to be delivered to all the patient’s cancer cells but the heterogeneity and inaccessibility of the target cells make this an elusive goal. To cure cancer these genes would have to be delivered to all the patient’s cancer cells but the heterogeneity and inaccessibility of the target cells make this an elusive goal.

**Fig 1—ERK and PRK (mean and SE) in breast tumours.**

Numbers of cases indicated above SE bar. Values as square-roots of nanomolar $K_d$ values.

- history. Breast tumour ER, ERK, PR, and PRK concentrations were measured with a Riaen Assay Systems kit (DuPont).
- There was a significant reduction in ERK and in PRK in the tumours of women with a family history of breast cancer. The results are expressed as the square-roots of nanomolar values, to normalise variances (fig 1). There was no significant association of ER or PR with family history (fig 2).
- 15 women had a first-degree family history of breast cancer in mother, daughter, or sister. The other women had affected aunts or cousins. There was no significant difference in the proportion of women with or without a family history who were premenopausal (23% and 19%, respectively).
- Although $K_d$ values are estimated in several laboratories, little has been published about their character or clinical usefulness. In one study, postmenopausal patients with high $K_d$ values tended to have shorter recurrence-free survival.
- Since $K_d$ reflects binding affinity between receptor and ligand, the "true" $K_d$ value should be identical within the same tissue in the same species. But the observed $K_d$ depends on assay method and receptor phosphorylation. Menopausal status also affects $K_d$ because of high endogenous oestrogen and progesterone levels in premenopausal women. However, there was no significant difference in the proportion of women with or without a family history of breast cancer who were premenopausal, so menopausal status is not a confounding variable in our study.

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- **Gene therapy for cancer**

Sir,—Dr Gutierrez and colleagues' review (March 21, p 715) was a useful introduction to some of the gene therapy ideas circulating in cancer research. However, in the context of tumour-cell-targeted gene therapy, insufficient emphasis was given to the important point that the genes must either reach all the target cells or destroy indirectly those tumour cells they cannot reach. Tumour-suppressor genes, MHC genes, and the vari-cella-zoster virus thymidine kinase gene proposed for virus-directed enzyme prodrug therapy (VDEPT) have no "bystander effect" and influence only the tumour cells to which they have been successfully delivered. To cure cancer these genes would have to be delivered to all the patient’s cancer cells but the heterogeneity and inaccessibility of the target cells makes this an elusive goal. 100% efficient delivery is not required for genes encoding secreted proteins that can (directly or indirectly) mediate the destruction of surrounding tumour cells. Bystander effects, apparently mediated through paracrine stimulation of host antitumour effectors, have been demonstrated after expression of interleukin-2 and interleukin-4 genes in rodent tumour models. Many other gene products may be capable of stimulating local antitumour immunity or generating locally cytotoxic "crossfire". Examples include other immunostimulatory cytokines, chemotactic peptides, antibodies, and toxins. Also, it may be possible to modify the VDEPT approach by engineering the genes to encode the drug–activating enzyme in a cell surface-associated or secreted form. Extracellular activation of the prodrug by enzyme derived from a small number of gene-transduced tumour cells might then lead to wholesale tumour destruction.

- The major obstacle to tumour-targeted gene therapy is inability to deliver genes efficiently to tumour deposits in vivo. Until gene transfer technology is up to this task the potential of this form of gene therapy cannot be tested, even in animal models. Virus vectors, the most promising vehicles for in-vivo gene delivery, are too large to cross the vascular endothelial lining of tumour blood vessels in numbers large enough to reach more than a small fraction of target cells. Vectors capable of replicating and spreading through a tumour may provide part of the answer to this problem but there are serious concerns about safety. Even on the most optimistic view, it is...