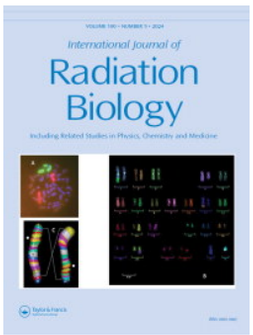

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Letter to the Editor

Biophysical models for the role of intracellular repair in the anomalous enhancement of neoplastic transformation by low doses of fission-spectrum neutrons at low dose rates: reply to the Letter to the Editor by P. R. Burch and M. S. Chesters

In previous papers, we and our co-authors reported that C3H mouse, embryo-derived cells designated 10T½ have an enhanced frequency of neoplastic transformation, induced by fission-spectrum neutrons, when they are exposed to low doses at low dose rates compared to high dose rates (Hill *et al.* 1982, 1984 b). Subsequent to these publications, we had an opportunity to expand on some of the biophysical implications and interpretations of our results in an exchange of Letters to the Editor (Barendsen 1985, Elkind and Hill 1985).

Burch and Chesters (1986) have now fitted two models to our data (Hill *et al.* 1984 b), the biophysical elements of the more general of which are based on ideas which are quite similar to our own (Elkind and Hill 1985). They propose that: single-track events have the potential for transforming cells; cells have the ability to repair these single-track events; the repair process has to be activated (or induced) by the radiation and it is assumed that this occurs linearly with dose; the system responsible for repair has limited capacity and is therefore saturable with dose; high dose rates are more effective in activating the repair process than low dose rates; the system responsible for repair can be inactivated (linearly with dose is assumed) more efficiently at a high dose rate than at a low dose rate; and lastly the inactivation of the repair system also saturates with dose.

Thus, Burch and Chesters require *first* that transformation is induced linearly with dose, *second* that cells are able to modify (e.g. to repair) single-track events, and *third* that the net amount of modification depends on dose rate as well as dose.

With the qualitative and conceptual implications of these ideas we agree as we had pointed out in our letter (Elkind and Hill 1985) and as had been discussed earlier (e.g. Elkind 1977, 1984, Hill *et al.* 1984 b). We note, however, that Burch and Chesters invoke what appears to be three separate single-track dependencies. The first registers the potentially effective lesion, the second induces the system which can repair the lesion, and the third inactivates the repair system if it is induced. These dependencies are required to be consistent with the microdosimetry of single-track events in the dose ranges of interest. But we note that fission-spectrum neutrons are accompanied by γ-rays (see discussion in Elkind and Hill (1985) and references therein) which may play a role in effecting one or more of the processes noted above without necessarily precluding a strong dependence on LET of the enhanced transformation at low dose rates. (See Han *et al.* (1980) and Hill *et al.* (1984 a) for the dependence of transformation frequency on dose protraction in the instance of γ-rays.) In addition, we note again the promoter-like activity which low-dose-rate fission-spectrum neutrons appear to have (Elkind 1984). A promoter like 12-*O*-tetradecanoylphorbol-13-acetate very likely initiates its action at the plasma membrane. Because of the irradiation geometry that was used (Hill *et al.* 1982) and

the flattened shape of a surface-attached $10T\frac{1}{2}$ cell (Lloyd *et al.* 1979), it is likely that a neutron secondary, which traverses the nucleus, will also traverse the plasma envelope. Hence, more than one process might be initiated by a single track.

The general model of Burch and Chesters has several interesting biophysical features which in turn lead to inferences along these lines. *First*, the frequency with which potentially transforming lesions are registered (the coefficient a in their notation) implies a target size appreciably larger than most genes, $\sim 1 \times 10^5$ base pairs. Hence, it would seem to be unlikely that the potentially transformed state results from a single base change in an oncogene as one might infer from the observations of Guerrero *et al.* (1984). *Second*, the high probabilities for the induction of the repair system are similar to the frequencies for the production of strand breaks in DNA. Indeed, the frequency at a high dose rate (β_H; Burch and Chesters 1986) is of the order of the sum of single- and double-strand breaks per cGy whereas at a low dose rate the frequency (β_L; Burch and Chesters 1986) is more like that of double-strand breaks alone. The inference follows that the well-known rapid repair of single-strand breaks, which is also observed after fission-spectrum neutrons (M. M. Elkind; and C. K. Hill and M. J. Peak; unpublished data), reduces the signal to turn on the repair system when the dose is protracted. And *third*, the probabilities of inactivation of the repair system (b_H and b_L; Burch and Chesters 1986) have targets of the order of size connected with cell killing. The suggestion follows from the last point that to inactivate the repair system the target to be hit must be appreciably smaller than that involved in its activation but also appreciably larger than the target for potentially transforming lesions.

The closeness with which the dose dependencies derived from the general model fit our data is impressive but as such is not a validation of the model, a point with which Burch and Chesters would probably agree. Nonetheless, the foregoing inferences relative to mechanism are worth noting even if viewed in only qualitative terms.

We pointed out in our last letter (Elkind and Hill 1985), and when our low-dose-rate neutron data were first published (Hill *et al.* 1984 b), that examples from *in vivo* experiments exist (Thomson *et al.* 1981, Ullrich 1984) which indicate that protracted exposures to fission-spectrum neutrons are more effective than exposures of short duration. In view of the variety of tumourigenic responses of different tissues in a given host, as well as the variations among different strains and species, it is probably too much to expect that data obtained with a single cell line *in vitro* will be applicable in all instances of tumour induction by fission-spectrum neutrons. Still, the qualitative agreement between our data and the *in vivo* results to which we have referred suggests that the mechanisms of oncogenesis by radiation *in vitro* and *in vivo* share important elements in common.

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