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Letter to the Editor

Correspondence re: H. Nagasawa and J. B. Little, Induction of Sister Chromatid Exchanges by Extremely Low Doses of α-Particles. Cancer Res., *52:* 6394–6396, 1992.

The recent article, "Induction of Sister Chromatid Exchanges by Extremely Low Doses of α-Particles," by Nagasawa and Little (1) shows dramatic changes in SCE[1] induction after exposure to ^{238}Pu α-particles. Calculations presented in the paper indicate that the vast majority of Chinese hamster ovary nuclei were not hit by even a single α-particle, raising the issue of what mechanism might lead to the observed increase. The authors speculate that autocrine signaling pathways activated by interaction with the α-particles with the cell membrane or cytoplasm might be involved.

In this regard, it is of interest to calculate what fraction of cells (as contrasted to nuclei) might be hit by these α-particles at the small doses (0.16–4.0 mGy) used. The authors quote an average nuclear area of 62.2 μm^2, which would indicate a nuclear diameter of about 7.9 μm. This value may be inserted into the relationship developed by Brenner (2) in which the mean number of tracks per unit area or per nucleus (θ) may be described by

$$\theta = 5(D)(d^2)/\text{LET (keV/μm)}$$

where D is dose (in Gy), d is the diameter of the object irradiated, and LET is the LET of the irradiating field, in this case the α-particles. For example, Nagasawa and Little state a value of 0.0004 α-particle track for a dose of 0.16 mGy. Solving the above equation for LET (not given in the paper of Nagasawa and Little), yields a value of about 124 keV/μm, which is in fairly good agreement with values cited by other investigators who have also used this ^{238}Pu source (*e.g.*, Ref. 3). In keeping with the suggestion of Nagasawa and Little, however, that cell membrane/cytoplasmic signal transduction mechanisms might be activated, it is worth calculating tracks/cell. Although the cellular area is not given by these authors, assume that the diameter of the cell is simply twice that of the nuclear diameter, which would make it about 16 μm (*i.e.*, 2 x 7.9 μm), and is not an unreasonable value for mammalian cells. This would serve to increase the mean number of tracks per cell by only a factor of 4 (*i.e.*, by the d^2 factor in the equation), which would mean that for the dose of 0.16 mGy cited above, there would only be about 4(0.0004) or 0.0016 track/cell. Even at the highest dose used (4.9 mGy), this would still indicate only about 0.0448 α-particle tracks/cell. Given that the vast majority of cells (let alone nuclei) are entirely missed by the α-particle beam, it becomes difficult to accept autocrine mechanisms as being responsible for the SCE effects seen in this study. Even at the highest dose used (4.9 mGy), the distances between α-particle tracks are much larger than the areas of the cells irradiated; consequently, most of the tracks and associated energy deposition events will occur in the noncellular regions between cells (monolayers are described as being 30–40% confluent). Because production of radiation chemical products such as free radicals dramatically decreases with increasing LET (4), this would seem to indicate that such chemical pathways are also not likely to be involved. Regardless, because the frequencies of SCE induction seem in the study of Nagasawa and Little to be in line with doses expected from typical levels of exposure to radon in the home, delineation of the processes involved would appear to be of significant importance.

John T. Leith
Department of Radiation Medicine
Brown University
Providence, Rhode Island 02912

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[1] The abbreviations used are: SCE, sister chromatid exchange; LET, linear energy transfer.

Reply

Dr. Leith raises several interesting points in relation to the observation in our recent *Cancer Research* article (1) that an increased frequency of sister chromatid exchange occurs in the nuclei of many cells not actually traversed by an α-particle. There are two issues, however, that deserve further clarification. Although the cells were 30–40% confluent at the time cultures were changed to isoleucine-deficient medium, they went through an average of 1.5 additional cell divisions during the subsequent 30–h incubation. Thus, at the time of irradiation, the cell monolayer was 80–90% confluent; the cells were essentially all in contact with each other though there was no crowding or overlapping of cells. As a result, most of the α tracks did traverse cellular regions. Second, although there may be a decrease in free radical production with high linear energy transfer radiation, significant quantities of hydroxyl radicals and superoxide anions will be produced by the associated δ rays.

We agree with Dr. Leith that it will be important to determine the nature of the processes involved in this unusual phenomenon, as well as the significance it may have for the effects of α-radiation *in vivo*.

Hatsumi Nagasawa
John B. Little
Department of Cancer Biology
Harvard School of Public Health
Boston, Massachusetts 02115

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