LETTER TO THE EDITOR

Paternal Irradiation and Leukemia in Offspring

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Lord and Hoyes (1) report the results from a series of mouse experiments in which the male mice were either injected with plutonium or exposed to γ radiation prior to the conception of offspring which were then treated with a known leukemogen, either methyl nitrosourea (MNU) or γ radiation. They conclude that paternal preconception irradiation can influence the susceptibility of offspring to a leukemogenic agent, although they acknowledge that the interpretation of the results is not straightforward [see, in particular, their Fig. 2 (1)]. We wish to examine the cautious suggestion by Lord and Hoyes (1) that their findings might be relevant to the cluster of childhood leukemia that has occurred in the village of Seascale, adjacent to the Sellafield nuclear facility in the county of Cumbria, England. They refer to a paper by us (2) in this respect, but they do not fully discuss the considerable difficulties facing such a suggestion.

In a case–control study, Gardner et al. (3) found a statistical association between relatively high recorded doses (≥100 mSv) of external radiation accumulated by fathers before the conception of their children while working at Sellafield and the level of leukemia in these children. They suggested (3) that this association could account for the excess of childhood leukemia in Seascale. Subsequently, however, it was shown that the doses of paternal preconception radiation associated with births in Seascale represented less than 10% of the collective paternal preconception radiation dose for children of Sellafield workers, whereas there was no comparable excess of childhood leukemia in the district outside Seascale (4, 5). Further, the association between paternal preconception irradiation and childhood leukemia in Seascale was statistically highly incompatible with the lack of such an association in Cumbria outside this village (6–8). Detailed studies have demonstrated that there is no association between paternal doses due to internally incorporated radioactive material and childhood leukemia either at Sellafield (6, 7, 9) or elsewhere (10).

No occupational exposure at Sellafield has been identified (including exposure to radionuclides that might irradiate the testes) that could account for the effective confinement of the excess of childhood leukemia to just the offspring of Sellafield workers born in Seascale (6–9). All this has led to the speculative suggestion that paternal preconception irradiation has increased the susceptibility of children to some specific leukemogen that is effectively restricted to Seascale, and it is this idea that Lord and Hoyes (1) address. There are a number of serious objections to this proposal.

First, the rate of radiation-induced events transmitted through the germ-line that predispose to this single end point (childhood leukemia) would have to be, at 13.2 × 10−7Sv, some 80 times greater than the accepted rate of radiation-induced mutations for all dominant effects in the first generation (11–13). Although Lord and Hoyes (1) point to the possibility of epigenetic processes playing some role, it would be most unusual if the effects of such a high rate of transmitted events had not been observed in any of the many studies that have now examined paternal preconception irradiation and childhood leukemia, whether in Cumbria or the rest of the world. The idea that paternal preconception irradiation affects only sensitivity to some Seascale-specific leukemogenic agent is stretching credibility to its limit.

Second, the strength of the interaction between paternal preconception irradiation and the putative “Seascale co-factor” required to produce an excess relative risk coefficient for Seascale that is appreciably greater (by more than two orders of magnitude) than that for Cumbria outside Seascale would be remarkable (8). The interaction would have to be substantially greater than multiplicative, and such extreme effect modification is implausible.

Third, notable excesses of childhood leukemia have been found at North Egremont, 8 km from Sellafield, and at West Thurso near the Dounreay nuclear facility in Scotland (14). Many children of nuclear workers were born in these two communities. In fact, the collective and mean individual paternal preconception radiation doses associated with births in North Egremont are greater than those associated with Seascale births (14). However, none of the four cases in North Egremont and only one of the six cases in West Thurso was associated with paternal preconception irradiation (14). It seems extraordinary that if paternal preconception irradiation confers the degree of enhanced susceptibility to leukemia to account for the Seascale cluster, then whatever factor might be producing the excess cases in North Egremont and West Thurso is not affecting the many supposedly susceptible children associated with paternal preconception irradiation in these communities, but those children whose fathers were not exposed.

Whatever might be the explanation for the findings of Lord and Hoyes (1), it is difficult to conceive of how the major obstacles to an interpretation involving paternal preconception irradiation of workers at Sellafield and some Seascale-specific leukemogen can be overcome. Compelling evidence now exists for an infective basis for childhood leukemia, and excess cases have been found in situations where unusual infective patterns are inferred to exist, but where exposure to radiation is normal (15). Population mixing in Seascale is known to be highly unusual. The parsimonious conclusion is that the Seascale cluster fits into this background of evidence for an infective cause of childhood leukemia, without the need to invoke paternal preconception irradiation as a material contributory factor (15).

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